Supplement: Detailed description of the relations between CVD and Mental-Ill-Health ***submitted 05.12.2006

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The idea that mind and heart are immediately related has a long cultural tradition and is even embedded in language as terms like “heartache”, “broken heart” or “heart-pounding situation” demonstrate. In the past decades considerable efforts were made to systematically uncover the psychobiological background of these perceptions. An obvious link between both domains are the shared risk factors, which are described in detail in other chapters. This part of the report is focussed on the direct relationship between both domains. It reports about a growing scientific knowledge about the bi-directional relationship between cardiovascular diseases (CVD) and mental-ill-health, which can be summarised into two main statements:

- ➔ Mental-ill-health is an independent risk factor for cardiovascular disease and mortality. The strength of the association is of similar magnitude to that of standard risk factors such as lack of physical activity or high cholesterol.
- ➔ Coronary heart disease can have adverse effects on the mental health of patients. For instance, while in the general population the prevalence of depression ranges from 3 to 10%, it is consistently higher among patients with myocardial infarction, with one year incidence rates up to 25%.

Both directions are of high interest not only for basic research on the origins of heart and mental diseases, but also for public health, because an understanding of the underlying processes is crucial for a successful evidence based prevention. Starting with the first pathway, the nature of the relationship between the disease groups is explained in the following paragraphs.

1.1 What is the role of mental-ill health in the causation of CVD?

Psychological phenomena like depression or anxiety not only impair a person's mental well-being. According to a large number of studies they could also be considered as risk factors for cardiovascular diseases. For example, Hemingway & Marmot (1999) concluded in their systematic review of prospective cohort studies that evidence exists for depression, anxiety, and type A personality being prognostic factors for CVD. Similar, Shah et al. (2004) stated in their review that there is a clear and convincing evidence that psychosocial factors, type A personality traits (anger, suppressed anger, hostility, antagonistic interactions, cynicism, and mistrust), social isolation, chronic life stress, depression and anxiety significantly contribute to pathogenesis and expression of coronary heart disease. Suls & Bunde (2006) have analysed several resent reviews and identified 3 affective dispositions - depression, anxiety,

and anger-hostility - as putative risk factors for coronary heart disease. As the examples show, a considerable number of mental problems are cardiovascular risk factors. To give a more detailed insight into those associations, three of the most relevant mental-Ill-health problems regarding CVD are now presented: (1) depression, (2) anxiety and (3) specific personality traits (e.g. Type A personality).

(1) Depression: A comprehensive body of research found associations between depression and cardiovascular disease (Hemingway & Marmot, 1999; Januzzi et al., 2000; Lett et al. 2004; Wulsin et al., 2003; Zellweger et al., 2004; Frasure-Smith et al., 2005). Particularly, people with depression are at greater risk for developing a coronary heart disease. This could be illustrated by a finding of the INTERHEART study, a large, worldwide project, which examined 11.119 patients with a first myocardial infarction and 13.648 healthy control persons from 52 countries in Asia, Europe, the Middle East, Africa, Australia, and North and South America (Rosengren et al. 2004). In comparison to unexposed participants, men and women who reported depression had a 55% higher risk of myocardial infarction, irrespective of region and ethical group. Furthermore, depression could negatively influences cardiovascular risk factors like hypertension, and worsens the prognosis after cardiac procedures in already ill persons (Kemp et al., 2003).

(2) Anxiety: Several studies have suggested that anxiety is associated with an increased risk of coronary heart disease in the general population. For example, in two prospective cohort studies (Kubzansky et al., 1998; Coryell et al., 1986) high levels of phobic anxiety were associated with an elevated risk of sudden cardiac death. Barger and Sydeman (2005) assessed in a cross-sectional study of a representative sample of U.S. adults, that generalised anxiety disorder was related to an unfavourable risk factor profile (i.e. smoking and hypertension). Esler et al., (2006) have shown that panic disorder commonly coexists with essential hypertension and the postural tachycardia syndrome. The mechanisms through which anxiety may increase the risk of CVD and cardiac events include hyperventilation during an acute attack, which could in turn induce coronary spasm, or an acute attack of anxiety triggering an episode of fatal ventricular arrhythmias.

(3) Personality traits: Personality traits may predispose to CVD, a hypothesis which in particular was tested for the concept of the “Type A” personality. In brief, Type A persons are characterised as highly ambitious and aggressive individuals with insatiable desire to achieve recognition and advancement, while their counterparts, the Type B persons are calm, laid back, and non-aggressive. Type A personality generally refers to hard workers who are often preoccupied with schedules and the speed of their performance. Type B personalities may be more creative, imaginative, and philosophical. One of the most influential reports about a relationship between those traits and CVD was an article from Siegel (1983) who presented empirical evidence, that type A personality is an independent risk factor for developing cardiovascular disease. But further research demonstrated, that the picture is not yet clear. Several researchers have criticized the concept in the sense that type A behavioural pattern is not a unitary phenomenon and it is possible that not all of its characteristics contribute equally to coronary risk. Myrtek (2001) analysed 25 prospective studies and concluded that there were no significant associations between the Type A behavioural pattern and heart disease at all. As a reaction to negative results, it has been

tried to identify the single components of type A behaviour, who were most strongly and consistently associated with heart disease. Evidence exists for increased cardiovascular reactivity (Siegman et al., 1994; Lepore, 1995; Drummond & Quah, 2001); increased incidence of ischemic heard disease, acute coronary syndromes, and total mortality (Goodman et al., 1996; Kawachi et al., 1996; Gallacher et al., 1999). Based on that results, it can be stated, that hostility and anger can be considered as the most 'toxic' components of the Typ A personality (Miguel-Tobal & Gonzalez-Ordi, 2005).

1.1.1 What are the psychobiological pathways between mental health and CVD?

How is it possible that mental processes have a negative impact on the cardiovascular system? To answer this question, it is necessary to look at the underlying biological und psychological pathways. Until today, research has identified several aspects of mental-ill-health which might explain their relationship. They can be summarized in two main pathways:

1. psychobiological mechanisms, including changes in the autonomic nervous, the hormonal and the immune systems;
2. behavioural mechanisms such as treatment adherence and health related lifestyles.

Pathway 1: Psychobiological mechanisms

Psychological diseases have their origin in mind and cognition, but they may affect many other systems of the human body. Dependent on their specific pathophysiology conditions of mental-ill-health for instance can provoke disturbances of the hormonal balance or elicit functional overreactions of organs.

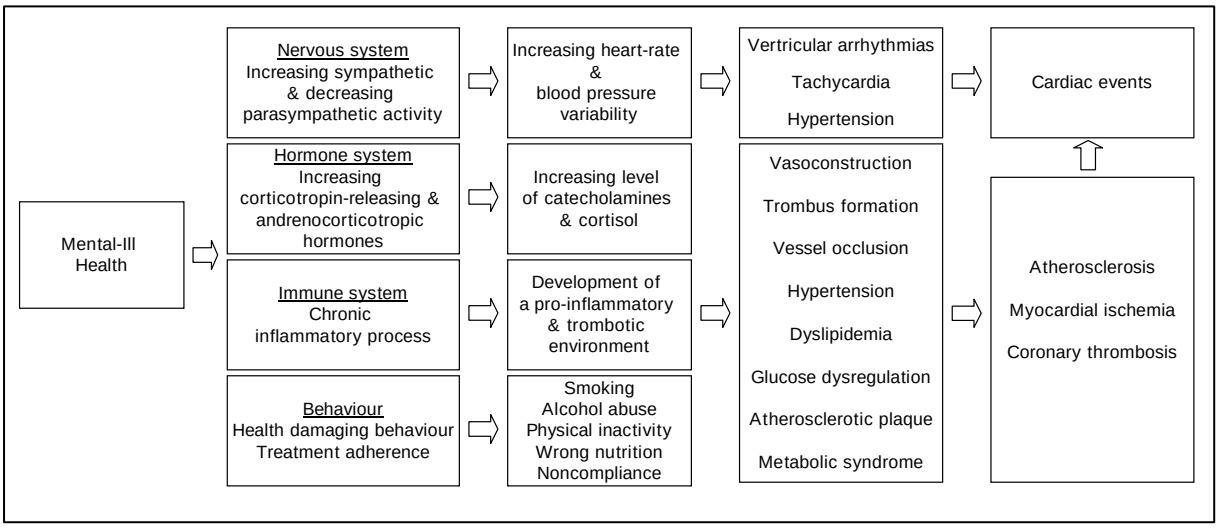

Fig. 1. Pathways from mental health to cardiac pathophysiology and manifest disease

In figure 1, some of the most important physiological correlates of mental diseases and their impact on cardiovascular health are shown. Four domains of physiological reactions to emotional states are listed in the figure and will be explained in more detail in the following sections: (1) activation of the autonomic nervous system, (2) hormone secretion, (3) changes in the immune system and (4) psycho-behavioural responses.

1.1.2 Autonomic function

Numerous studies provide evidence that MIH is associated with certain disorders of cardiac autonomic nervous system (ANS) function, in particular, with an autonomic neurocardiac imbalance characterized by increased sympathetic and decreased parasympathetic activity. Associated with this reactions are:

(1) a decreased heart rate variability (amount of fluctuation of the heartbeat-to-heartbeat differences), which increases risk of ventricular arrhythmias (irregular and rapid beating of the heart's main pumping chambers) and sudden cardiac death from ventricular fibrillation (Kibler & Ma, 2004; Gorman et al., 2000);

(2) a low-frequency power of blood pressure variability that have been suggested to reflect changes of central sympathetic nervous control. It has been shown, that increased daytime systolic blood pressure variability is associated with increased risk of sudden cardiac death (Kikuya et al., 2000) as well as stroke death (Gilmore et al., 2006);

(3) low baroreflex sensitivity, that leads to high blood pressure and predicts increased cardiovascular mortality (La Rovere et al., 1998).

1.1.3 Hormone system

Psychological distress, depression and anxiety could cause a hyperactivation of certain stress related parts of the hormonal system (in particular the hypothalamic-pituitary-adrenocortical axis). Some of the involved stress hormones like *cortisol* and *catecholamines* can cause an elevation of blood pressure and a faster heart rate. Blood flow is decreased, which may then increase the risk of an acute angina attack. Corticosteroids mobilize free fatty acids, causing endothelial inflammation and excessive clotting, and are associated with hypertension, hypercholesterolemia, and glucose dysregulation, a pre-stage of diabetes. Increased circulating lipids and endothelial shearing stress can lead to vascular damage and plaque formation. Increased level of catecholamines are also altering blood clotting and may lead to vessel occlusion. Moreover insulin and cholesterol levels are raising, both important CVD risk factors.

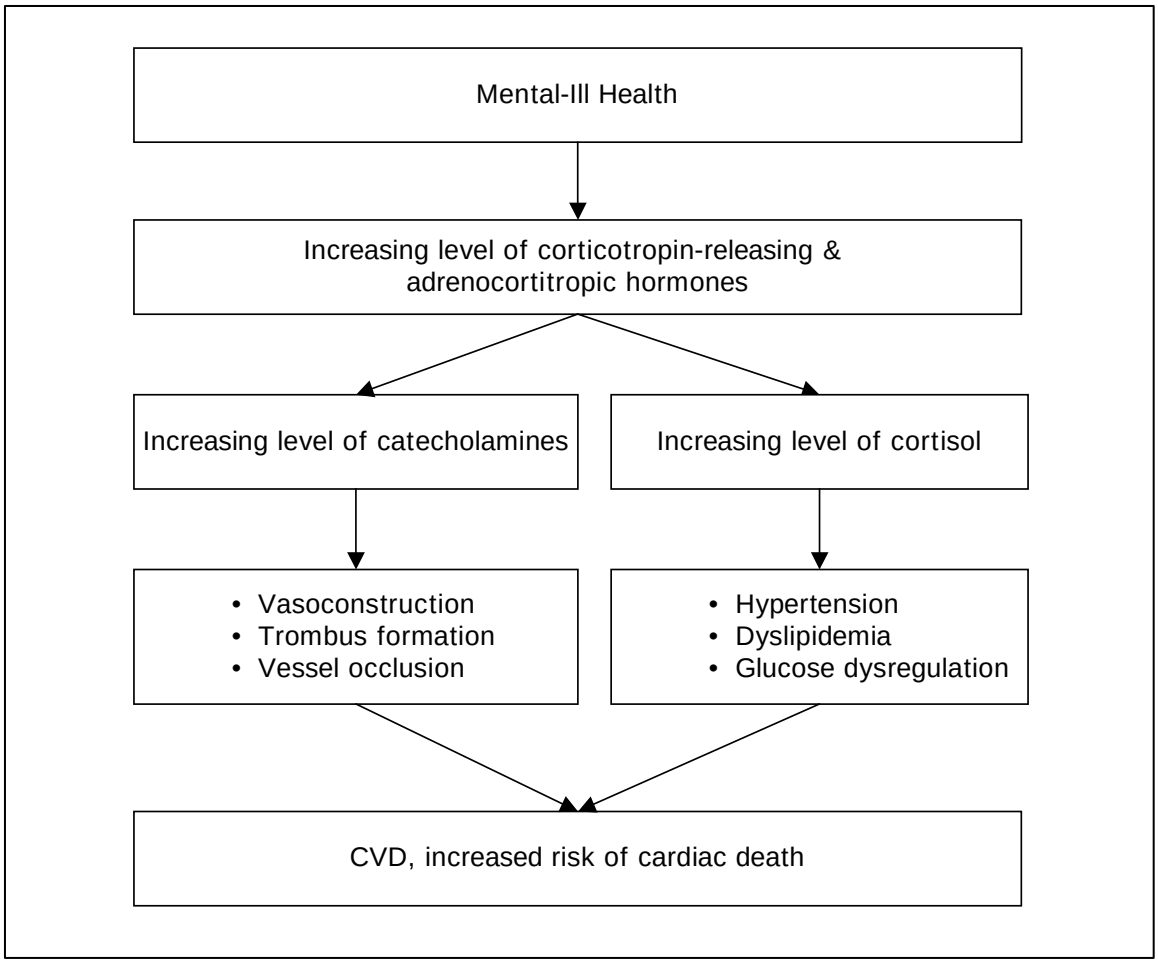

Fig. 2 The hormonal pathway

1.1.4 Immune system (Inflammation)

Inflammation may mediate the relation between metal-ill-health and cardiovascular disease. It is known that the immune system has a central role in all stages of atherosclerosis. Endothelial dysfunction, caused by endothelial inflammation, results in a breakdown in the anti-inflammatory and anti-thrombotic properties of the endothelium and could be one major step in the initiation of atherosclerosis. Consequent development of a pro-inflammatory and pro-thrombotic environment leads to increased recruitment of leukocytes, lipids, smooth muscle cells, fibroblasts, and platelets to the arterial wall. Repeated cycles of this process result in hyperplasia of the intima-medial layer of the vessel wall and the development of an atherosclerotic plaque. Particularly, C-reactive protein has emerged as a significant predictor of increased risk of atherosclerosis. Major depression also has been associated with elevated C-reactive protein levels. Thus, adverse cardiac outcomes and depression could be linked through pathways with C-reactive protein or other markers.

1.1.5 Behavioural mechanisms

Treatment Adherence

Mental problems predict poor adherence to prescribed regimens which is another mechanism linking mental-ill-health and cardiovascular disease outcomes. For example, in a meta-analysis about the effects of anxiety and depression on patient adherence (DiMatteo et al., 2002) the authors concluded that the relationship between depression and noncompliance was substantial and significant. Compared with nondepressed patients, the probability of noncompliance with medical treatment recommendations is 3-times higher in depressed patients (odds ratio of 3.03 (95% confidence interval, 1.96-4.89). Nonadherence to recommended lifestyle changes and medication regimes itself is associated with decreased survival for coronary artery disease patients (McDermott et al., 1997).

Lifestyle Factors

Mental problems and stress have an important influence on the health related lifestyle of a person, such as smoking habits, physical activity or alcohol consumption (Steptoe et al., 1998). Often, this influence is a negative one, in the sense, that risky behaviours are promoted under conditions of mental-ill-health. For instance, stressed individuals could try to reduce negative feelings by sedative and anxiolytic effects of nicotine. Another example is alcohol consumption as a psychological response to stress. Some studies have shown that depressed individuals with CVD may take poorer care of themselves, pay less attention to diet. In this context it is noteworthy, that certain adverse behaviours could themselves be understood as mental problems and might therefore be related to cardiovascular health even without the presence of other diagnoses like depression or anxiety. A prominent example is manifest alcoholism.

The following paragraphs briefly describe the relationship for major behavioural risk factors.

a) Tobacco consume, smoking cessation: Smoking behaviour is linked with the experience of adverse mood and stress. For example, smokers frequently report that they want to smoke most when they feel stressed (Jarvis, 2002). Kouvonen and colleagues (2005), analysing the data from the combined sample of two ongoing Finnish cohort studies (the 10-town study and the hospital personnel study), have found that chronic work stress is significant related to cigarette smoking. Also depression has found to be associated with an increased rate of smoking in patients with CVD and additionally may lower the success of smoking cessation programs (Glassman et al., 2001).

b) Nutrition: There is some evidence that mental problems can influence health through adverse changes in diet. For example, workers with constant time pressure may select the most convenient food available, with a reduction of dietary quality as a result. Or stress may alter the choice as well as the amount eaten of particular food. Stress or mood disorders could lead to reduced appetite and cause the energy dense snack food choice. Huether and

colleagues (1998) have pointed out that selective carbohydrate consumption or prolonged food restriction can result in increased serotonin function that could be an unconscious manipulation of mood by dietary selection.

c) Alcohol consumption: Recently, researchers have clarified the connection between alcohol and mental health (Steptoe et al., 1998). Some authors have pointed at the association of heavy alcohol consumption with depression (Bott et al., 2005). Several studies found that alcohol induces the stress response by stimulating hormone release, which can have damaging effects on the cardiovascular system. It is noteworthy, that a number of studies have suggested that low to moderate alcohol intake is associated with a lower incidence of atherosclerotic cardiovascular events, such as myocardial infarction. These benefits of moderate alcohol intake may be related to increases in high-density lipoprotein (HDL) and apolipoproteins A_1 and A_2, antioxidant effects, and reduced platelet aggregability. However, higher intake levels are associated with increased risk for hypertension, cardiomyopathy and other cardiac complications.

d) Physical activity: It was purposed, that physical inactivity might be a result of mental-ill-health. For instance, Bonnet et al. (2005) have examined the association of anxiety and depression with healthy behaviours in a large population of subjects at risk of cardiovascular disease, and found that both anxiety and depression were significantly associated with physical inactivity in men and women.

1.2 What is the role of CVD in the causation of mental-ill-health?

Due to massive research efforts in the past 20 years, the role of mental health as a risk factor for CVD is increasingly better understood. Although less is known about the other way around, the existing evidence gives a more and more consistent picture: It can be stated, that cardiovascular diseases could have an severe adverse effects on the mental health of patients: up to 20% of individuals experience a major depressive episode within a few weeks after an acute cardiovascular event, with a further 25% having minor depression or dysthymia (Carney et al., 1987; Steptoe & Whitehead, 2005). This imposes a heavy burden not only for the mental well-being of patients, but also for the prognosis of their cardiovascular disease. According to meta analyses, cardiac patients with a manifest depression had more then a twofold higher mortality than patients without depression (Bath et al., 2004; van Melle et al., 2004). Further studies have shown that depression is common among patients recovering from a myocardial infarction. For example, Bush et al. (2005) stated in their review that major depression, diagnosed by a structured clinical interview, is reported in about one of every five patients hospitalized for MI. The reported prevalence of potentially significant symptoms of depression varies more widely (range 10 to 47 %).

Depression is also common after stroke. The prevalence of poststroke depression (PSD) is high - more than half of the ischemic stroke patients report a depression within the first 3-month following the event (Kauhanen, 1999).

Apart of depression, also cognitive functions like dementia or Alzheimer's disease are negatively influenced by cardiovascular disease. For example, the findings from the Washington Heights study point on a fivefold increased risk of developing a dementia in the 4 years after an ischemic stroke (Tatemichi et al., 1994). Moreover, cerebral atherosclerosis is associated with a higher risk of Alzheimer's disease (Honig et al., 2005). In the Rotterdam study, 284 subjects with dementia of less than 3 years duration were compared with 1698 persons without dementia. One of the findings of this study is that atherosclerosis is associated with both vascular dementia and Alzheimer's disease and that the prevalence of both increased with the severity of atherosclerotic disease (Hofman et al., 1997). The association between hypertension and dementia has been examined in the Göteborg study, a longitudinal population based examination of a cohort of 382 subjects without dementia at age 70. The researchers found that participants who developed dementia at ages between 79 and 85 had significantly higher systolic and diastolic blood pressure at 70 and 75 than those who did not develop dementia (Skoog et al., 1996).

Mental health problems in patients with CVD are having both neurobiological and psychopathological dimensions. In the following chapter we will briefly introduce those relationships.

1.2.1 Neurobiological mechanisms

Many different vascular pathologies could lead to cognitive impairment or vascular depression, including cerebral thrombosis, cardiac embolism, and hemorrhage. The neurobiology of mental diseases and cognitive impairment is quite complex and it is not easy to identify those components which are related to an underlying cardiovascular disease, but the following processes are currently under discussion:

(a) Atherosclerosis is a risk factor for cerebral ischemia (a process, when parts of the brain do not receive enough blood flow to maintain normal neurological function). It is known, that arteriosclerosis is increased in cases with vascular dementia, which is most commonly associated with widespread small ischemic or vascular lesions (microinfarcts, lacunes) in important brain regions (thalamus, hippocampus) (Jellinger; 2002). It was suggested that symptoms of vascular depression are also associated with cerebrovascular lesions (Alexopoulos et al., 1997).

(b) Chronic hypertension is associated with several pathologies which may lead to cerebral infarction and cognitive deficits. Hypertension causes a shift in the cerebral blood flow autoregulation curve to the right: thus, a relative decrease in the blood pressure, due to a hypotensive episode for example, is likely to lead to a greater than expected decrease in cerebral blood flow in the watershed zones (hypoperfusion problem). Furthermore, hypertension is associated with arteriosclerosis (see above). Moreover, chronic hypertension or sudden elevation of blood pressure may cause cerebral haemorrhages that could also affect cognitive abilities.

(c) Chronic hypoxic injury to the brain, which could promote degenerative processes in brain (for example Alzheimer's disease).

1.2.2 Psychopathological mechanisms

Often people suffer from adverse emotional reactions subsequent to the manifestation of CVD. Patients may feel depressed because CVD has forced them to give up activities they enjoy or restrict working life, they may live in fear of the next painful attack or have manifested fear of dying in the face of a life threatening situation. Those associations are illustrated by a number of studies who indicate that depression frequently appears as a consequence of heart disease and/or heart disease surgery. But the psychopathological response to the disease is highly variable and depends on personal characteristics and the psychosocial environment of the patients. The nature of the underlying cardiovascular disease is a moderating factor as well. It is documented, the hazardous of the diagnosis, the perceived ability to control the symptoms and the influence of the diagnosis on daily life activities determine whether mental health problems occur or not. Table 1 gives an overview of common psychological reactions to CVD (Smulevich et al., 1999). Three syndromes are described (1) neurotic syndrome, (2) affective syndrome and (3) pathocharacterological development of personal traits. They are grouped according to the subjective relevance a patient ascribes his illness (high vs. low).

A neurotic syndrome with high subjective importance of the diagnosis is characterised by obtrusiveness, hypochondria, restriction of work and physical activity, limitation or exclusion of any potentially stressful information and preference for passive leisure time activities. Neurotic syndrome with low subjective importance of the diagnosis could be described as a combination of permanent somatic anxiety with „neurotic denial“ of the disease and poor adherence to treatment or recommended lifestyle changes. An affective syndrome with high subjective importance of the diagnosis could emerge as a hypochondriac depression with pessimism, anxiety, hopelessness and reduction of physical activity. In the opposite, affective syndromes with low subjective importance of the diagnosis proceeds with euphoria, and an inadequate positive appraisal of the disease severity and its consequences.

Another possible reaction to disease - mostly after hard cardiac events - is a pathocharacterological development. Patients with high subjective importance of the diagnosis have a high motivation to overcome the disease. They may try to cope with illness for example through increased (intensive) physical activity or by “modernisation” of the therapy (often against medical recommendations). An opposite reaction is the pathological denial of the disease, i.e. the tendency to minimize the symptom’s gravity or deny the hazardous consequences of the disease.

Table 1: Typological differentiation of psychological (“nosogenic”) reactions (Smulevich, 1999)

	Metasyndromal level	
Syndromal level	**High subjective importance of the diagnosis**	**Low subjective importance of the diagnosis**
Neurotic syndromes	Phobic syndrome	Narcissistic syndrome
Affective syndromes	Reactive depression	Reactive mania
Pathocharacterological development	"Rigid hypochondria"	"Health hypochondria"

1.3 Conclusion

The relationship between mental-ill-health and cardiovascular disease is a complex issue, but a growing number of studies have contributed to the understanding of the interrelations between the both. A majority of these studies found higher rates of cardiovascular diseases in persons with mental-ill-health like major depression or anxiety. Less research has been conducted to answer the question whether a pre-existing CVD influences the onset of MIH, but in general substantial associations were observed. Nonetheless causal inference has to be made with caution, because research is challenging in this field and deserves complex designs. Studies might therefore be subjects to different forms of bias. Furthermore, it has to be noticed, that not all studies confirm the existence of direct associations between the diseases. More research is therefore needed to clarify inconsistencies. Additional information is also needed regarding the underlying mechanisms. Some plausible pathways have been uncovered yet– and described in this report – but knowledge is far from being complete.

In conclusion, the existing knowledge about the multiple interrelations between mental-ill-health and cardiovascular disease, shed light on the mechanisms involved in the onset, development and prognosis of such disorders. The relevance of *working life* in this context is obvious, since adverse working conditions – in particular psychosocial work stress – are risk factors for mental-ill-health as well as for cardiovascular disease. An improvement of working conditions might therefore have multiple benefits because the prevention of mental diseases might have an additional positive effect on cardiovascular risk and vice versa.

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