UiT The Arctic University of Norway

The Faculty of Health Sciences

Can Thoughts Make You Physically Ill?

Cardiovascular Complications of Neuroticism

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Foreword

The fact that physical health can have an impact on emotional wellbeing hardly comes as a surprise to anyone. But what about the other way around? My interest towards this topic originated from a series of events during the past few years. For instance, a couple of years ago, I had the opportunity to work at a pain clinic. At the time, I got to learn about the role of adverse life experiences as a risk factor for developing chronic pain conditions. According to my understanding, the connection between chronic pain and psychological well-being was indeed bidirectional. I was interested in learning about the mechanisms behind this dynamic.

From there, I started to wonder more about how diverse aspects of psychological well-being influence physical health. I knew I wanted to explore it in some way in my thesis, but I was not certain which point of view to adapt or how to operationalize the exposure. Throughout the writing process I received helpful feedback and advice from my mentor, associate professor Ole K. Grønli at the Arctic University of Norway. We decided to opt for high neuroticism as the exposure and the outcome got eventually narrowed down to cardiovascular disease. Therefore, this paper investigates the biopsychosocial implications of personality, more precisely the study of high neuroticism as a potential risk factor for developing cardiovascular disease.

During the writing process someone questioned me about the topic of choice; *but is it not stigmatizing to study if someone's personality increases the risk of somatic illness?* Everyone may not agree, but I personally believe that the point of reference is ultimately a hopeful one. As a side point, although increased neuroticism itself does not automatically indicate psychopathology, the various connections between high neuroticism and affective disease are also explored in my thesis. Additionally, this paper provides insight into some of the potential underlying origins of this personality trait. Although perhaps influenced by an optimistic worldview, I believe as famously expressed, that the truth – in all its agony – may lead the pathway to freedom.

Lastly, I would like to thank my mentor Ole K. Grønli from the Institute of Clinical Medicine at the University of Tromsø for assisting me in the writing process.

Milla Lehtonen, 27.05.2024

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Abstract

Introduction: Cardiovascular diseases are among the leading causes of morbidity and mortality. In recent decades researchers have identified psychological factors which could influence the cardiovascular risk profile. Alongside traditional cardiovascular risk factors such as hypertension and hypercholesterolemia, personality traits may contribute to behavioral and immunological effects which could influence the risk of developing cardiovascular diseases.

Purpose: The purpose of this literature review is to examine if high neuroticism, as described in the Big Five personality model, causes an increased risk of cardiovascular diseases (coronary heart disease and stroke).

Material and methods: Two separate literature searches were conducted in MedLine (22.08.2023) and APA PsycNet (26.01.2024). In total, 139 records from the literature searches were screened and assessed for eligibility. Cohort studies published during the past 10 years which include over 1000 participants were eligible for the current review. A total of 10 cohort studies or reviews of longitudinal studies were included in the final analysis. The risk of bias was assessed with some of the principles described in the GRADE evaluation method.

Results: In total, 7 out of 10 research papers found a small yet significant link between high neuroticism and the risk of developing cardiovascular disease. The HR for MI/CHD ranged between HR 1.03 (CI 1.02-1.04) and HR 1.14 (CI 1.07–1.21) in the three largest study samples included. The results indicate a small but statistically significant neuroticism mediated risk. High conscientiousness had a protective effect against heart disease. The results among stroke risk were inconsistent and did not provide sufficient evidence for indicating an association.

Conclusion: This literature review found a link between high neuroticism and an increased risk of developing myocardial infarction and coronary heart disease. Nevertheless, the risk was rather small in comparison to the risk imposed by the traditional risk factors. The evidence for personality mediated stroke risk was insufficient.

Abbreviations

ACC: Anterior cingulate cortex

ACTH: Adrenocorticotropic hormone

BFI: Big Five Inventory

BMI: Body mass index

CHAP study: *Chicago Health and Aging Project* study

CHD: Coronary heart disease

CRH: Corticotropin releasing hormone

CT model: continuous time model

CVD: Cardiovascular disease

EPI-Q: Eysenck Personality Inventory questionnaire

GAD-2: Generalized anxiety disorder 2-item questionnaire

HF: Heart failure

HRS: *Health and retirement study*

HRV: Heart rate variability

IPIP: International Personality Item Pool

LISS: *Longitudinal Internet Studies for the Social Sciences*

MDI: Major Depression Inventory

MI: Myocardial infarction

MIDI: Midlife Development Inventory

MIDUS study: *Midlife in the United States* study

NAS: *Veterans Affairs Normative Aging Study*

NEO-FFI: NEO Five-Factor Inventory

NESDA: *Netherlands study of Depression and Anxiety*

NESDO: *The Netherlands study of depression in older persons* (sic)

NHATS: *National Health and Aging Trends Study*

PART study: *Psykisk Hälsa, Arbete och RelaTioner* study

PHQ-2: Patient health questionnaire 2-item

RI-CLPM: Random Intercepts Cross-Lagged Panel Model

SATSA: *The Swedish Adoption/Twin Study on Aging*

SSP*:* Swedish scale of personality

US study: *Understanding Society study*

WLS: *Wisconsin longitudinal study*

1 Introduction

1.1 General introduction and purpose of the study

Cardiovascular diseases are one of the leading causes of morbidity and mortality. During the recent decades much attention has been directed towards identifying, preventing, and treating risk factors for cardiovascular diseases. Preventing and treating traditional risk factors including smoking, obesity, diabetes, hypertension, hypercholesterolemia, sedentariness, poor diet, and high alcohol consumption have had a large impact on preventing adverse cardiovascular outcomes in the general population. Alongside an improvement of treatment options, these measures have contributed to a dramatic decrease of disease burden from cardiovascular diseases. According to the Norwegian Institute of Public Health the incidence of myocardial infarction has decreased remarkably since the 1970's. Additionally, the mortality has been reduced by half during the past two decades in Norway (1).

Interestingly, alongside the traditional risk factors, research has also identified emotional and psychological risk profiles of heart disease. Stress is a renowned risk factor for cardiovascular diseases. Likewise, people suffering from affective disorders such as anxiety and depression face an increased risk of cardiovascular diseases (2). There is also evidence for that adverse childhood experiences, such as early traumatic events increase the risk of somatic health conditions, including CVD (cardiovascular disease) (3). Perhaps one of the most literal characterizations of the mind-heart connection which springs to mind is Takotsubo cardiomyopathy, or Broken heart syndrome, where an individual can develop signs of heart failure typically proceeded by a period of intense stress (4).

An interesting point of view is whether personality could influence the risk of developing somatic diseases. One of the most famous definitions of personality is that personality is a characteristic pattern "of thoughts, feelings and behaviors" (5, 6) On a general level personality is considered a relatively stable set of these characteristics which tend to guide our behavior across different contexts. However, there is also some evidence for a certain degree of plasticity to personality across the lifespan (7). The Big Five personality model is one of the most renowned models for classifying the different components of personality. The Big Five model is presented in more detail under "1.4 Introduction to the Big Five personality model".

One of the traits included in this model is neuroticism. This is a personality trait which describes an inclination towards a tendency to experience higher levels of negative emotion. In

accordance with previous examples, one could hypothesize that increased negative emotion could be associated with the development of heart disease and stroke. The purpose of this literature review is to examine whether personality, more specifically high neuroticism is associated with an increased risk of acquiring cardiovascular diseases (coronary heart disease/myocardial infarction and stroke).

1.2 Cardiovascular diseases

Cardiovascular diseases involve diseases of the heart and the circulatory system, including but not limited to coronary heart disease/myocardial infarction and stroke. In this review cardiovascular diseases are defined as these three outcomes which are among some of the most common types of CVD. Traditional risk factors for cardiovascular disease are divided into modifiable factors, such as smoking, obesity, diabetes, hypertension, hypercholesterolemia, sedentariness, poor diet and high alcohol consumption, and non-modifiable factors such as age, sex, family history and ethnicity, which impact the total cardiovascular risk profile (8). Despite a significantly reduced incidence rate and mortality rate during the past decades (9), cardiovascular diseases still causes approximately 200,000 patients to be in contact with specialist health care annually in Norway (8).

Stroke is defined as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" (by World Health Organization) (10). Stroke can be attributed to either ischemic or hemorrhagic etiology with the former accounting for approximately 85% of all cases. In addition to the traditional cardiovascular risk factors, atrial fibrillation is a risk factor for ischemic stroke as it is often linked to thromboembolic events. Risk factors for hemorrhagic stroke include hypertension, cerebrovascular amyloid deposition, and vascular malformations. Hemorrhagic stroke can also be attributed to iatrogenic causes such as use of anticoagulant drugs (11).

Coronary heart disease, including its subtype myocardial infarction, is a manifestation of compromised oxygen delivery to the cardiac muscle. Coronary heart disease is associated with atherosclerosis which can generate vascular stenosis and the formation of thrombi. In case the blood supply to a coronary artery is cut off or partially blocked due to an occluding element blood supply must quickly be re-established to avoid damage to the cardiac muscle. Ischemic damage to the heart will lead to increasing levels of troponins. Additionally, a myocardial

infarction will often display characteristic signs of ischemia on an ECG, including ST-segment elevations, -depressions and/or T-inversions in the leads corresponding with the damaged area. Ischemic heart disease shares many of the common traditional risk factors with ischemic stroke (9).

Throughout the years a multitude of risk models have been developed to give account for different aspects of cardiovascular risk assessment as well as to help clinicians choose between preventative treatment options. The NORRISK2 calculator is an example of a widely used risk-estimation tool in the Norwegian population. Traditional risk factors including age, gender, smoking status as well as information on blood pressure, cholesterol levels and family history of MI are plotted into the calculator. Thereafter, this model provides an estimate of the risk of developing myocardial infarction or stroke during the next 10 years (12). The Norwegian national guidelines also provide additional suggestions for the prevention of CVD in patients with diabetes and other complicating factors (13). Specialized tools have been created with regards to different issues, such as the CHA2DS2-VASc calculator which is used to estimate the risk of stroke in the presence of atrial fibrillation (14).

1.3 The ABCD personality classification and cardiovascular risk

The possibility for a personality based cardiovascular risk profile sparked interest already around the mid-twentieth century. At the time it was initially announced that type A personality is an independent risk factor for coronary heart disease (15). The type A personality has traditionally been defined with terms such as “impatient”, “ambitious” and “competitive”. While efficient and high performing, the type A personality has also been associated with resigning to aggression and hostility. During the late twentieth century the preliminary claim that personality type A is associated with cardiovascular disease begun to falter as studies with conflicting statements started to appear. In the light of the newer publications the earlier studies were subjected to lots of criticism. It was questioned whether it is type A personality or its confounding traits, such as sensitivity to stress, which is linked to the cardiovascular risk (16).

Additionally, other aspects of the ABCD-personality classification have received a lot of attention in relation to cardiovascular risk. Particularly type D personality, which is generally characterized by timidness and negative emotion (17). Despite efforts to prove an association between a “distressed personality” and adverse cardiovascular outcomes, this type of research has also faced plenty of criticism (18). First and foremost, type D personality describes a set of

characteristics which constitute the personality type. It may not be the optimal approach to analyze the effects of a "collection" of personality traits. For instance, while negative affectivity and social inhibition describe type D personality, a much more accurate point of reference may be to analyze separately the effects of neuroticism and introversion. In light of these findings, much research on personality has shifted its focus from the ABCD-classification to the five-factor model (19).

1.4 Introduction to the Big Five personality model

The Big Five model (see Figure 1) approaches personality from five different dimensions: *agreeableness*, *openness*, *conscientiousness*, *extraversion*, and *neuroticism*. In accordance with this model, personality represents a unique composition of these five traits, where each trait exists on a spectrum between two opposing ends, for example agreeableness-disagreeableness or extraversion-introversion (20). Further along, each of these dimensions may be divided into 6 different subcategories or so-called facets according to the Revised NEO Personality Inventory facet scale. These facets describe a combination of characteristics which compose the five basic traits (21).

A quick summary of the 5 main domains (for a summary of the individual facets, see Figure 1):

- **Agreeableness** reflects a person's willingness to engage in conflict. A highly agreeable person could come across as friendly, polite, and compromising, whereas someone who exists at the other end of the agreeableness spectrum would be described as more disagreeable.
- **Openness** describes a person's attitude towards new experiences and ideas. An individual scoring high in openness would be more likely to relate positively to engaging in new activities than a less open, more cautious individual. Therefore, high openness may be a contributor towards engaging in risk taking behaviors.
- **Conscientiousness** tells something about the way we relate to responsibility and self-discipline. A highly conscientiousness person could be more likely to for instance responsibly follow instructions than a less conscientiousness, more careless person.
- **Extraversion** describes the way a person relates to social interaction and solitude. A greater need for social stimuli and social seeking behaviors could reflect a personality that is characterized by an increased degree of extraversion in comparison to a more introverted personality.

- Lastly, **neuroticism** describes an inclination towards responding to authentic or perceived adversities with negativity. A high level of neuroticism is linked to more negative emotions, whereas low levels of neuroticism is associated with emotional stability and confidence (22).

In previous research, many associations have been made between personality traits and physical as well as psychiatric health conditions. Therefore, taking account for personality traits may be clinically relevant in certain settings. This study will specifically focus on the personality trait neuroticism. In this paper the use of "neuroticism" means "high levels of neuroticism" if not otherwise specified. Neuroticism has been of particular interest in many studies which examine the associations between personality and psychiatry. This personality trait has been associated with a range of adverse psychiatric outcomes. A systematic review article from 2021 linked neuroticism to the risk of developing affective disorders (23). Neuroticism has also been suggested to be worth noting as a possible risk factor related to somatic health (24), for instance in association to the risk of developing functional dyspepsia (25) or complications of type 1 diabetes (26).

Allostatic load is an important concept when talking about somatic health within a psychiatric context. Allostatic load is defined as "the cost of chronic exposure to fluctuating or heightened neural and neuroendocrine responses resulting from repeated or chronic environmental challenges that an individual reacts to as being particularly stressful" (27). The possible adverse health effects of allostatic load have been studied across and associated with a wide range of both somatic and psychiatric conditions (28). It has been suggested that this type of stimulus may impose multiple changes on a cellular level and consequently be linked to the development of somatic diseases (27). Emotional stress has for instance been shown to be a significant risk factor for cardiovascular disease (2, 29).

Meanwhile, the link between neuroticism and somatic health was investigated in a review article from 2009 (24). The authors suggest that neuroticism itself may be a considerable risk factor for morbidity and mortality. Multiple mechanisms account for this: risk factors relating to inheritance, stress related mechanisms, dysregulated nervous system activity, social behavior, as well as hormonal and immunological etiology. All of which potentially could lead to the development of somatic disease. For instance, neuroticism is linked to a sensitivity to experience negative emotion or feel emotional stress. These physiological consequences of

negative emotion mediated stress could then again be associated with the development somatic conditions (24).

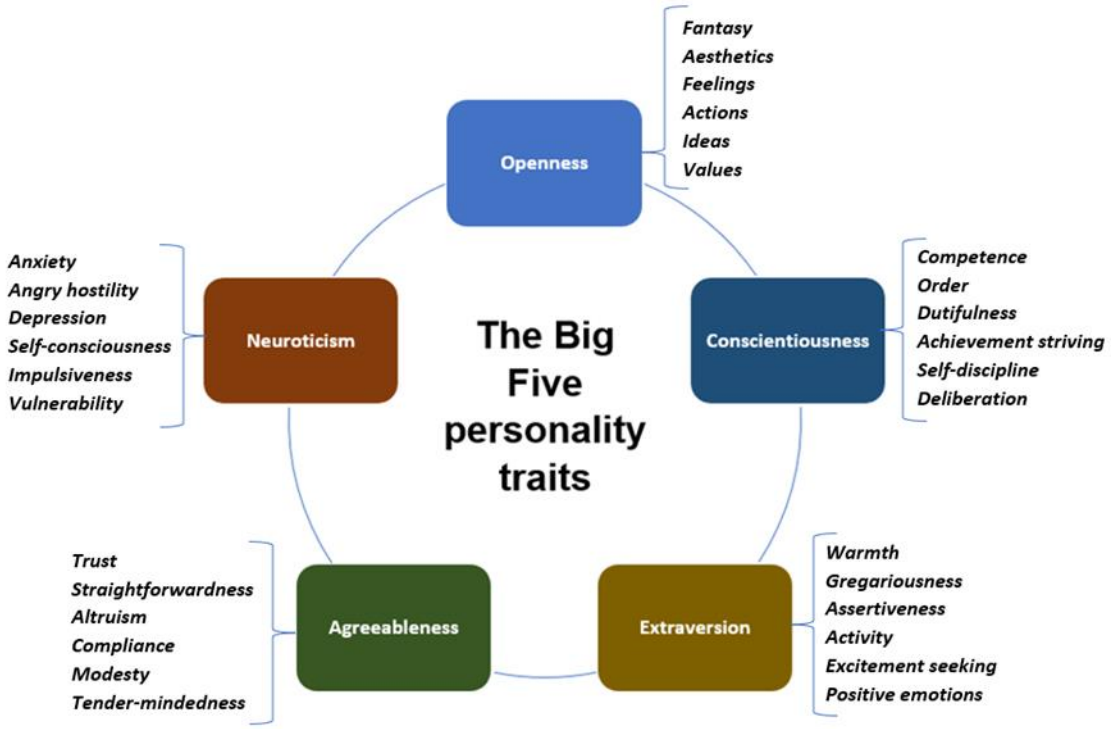

Figure 1. *Presentation of the Big Five personality traits and their facets. This figure is based on the study "Domains and facets: hierarchical personality assessment using the revised NEO personality inventory" from Costa and McCrae, 1995. All of the adjectives that describe each five dimensions are directly derived from a list of adjectives found in this study(21).*

1.5 Personality measurement

Neuroticism levels can be assessed with several different methods, including questionnaires, interviews, and clinical observation. Costa and McCrae were among the leading scientists who developed the Big Five model in the latter third of the 20th century. Their NEO-PI or the **NEO Personality Inventory** is among the most recognized personality tests to this day. The revised version includes 240 questions which assess the structures of personality (21, 30). The components measured in the NEO-PI are illustrated in Figure 1. This personality test is well documented in the literature and has demonstrated a good predictive value across different studies (31). Throughout the years more concise versions of the NEO-PI which take shorter time to complete have been created. These include the NEO-FFI (**NEO five factor inventory**) with only 60 questions which assess the level of the five basic traits (32).

Before the development of the Big Five model, researcher Hans Eysenck had initially proposed that personality could be illustrated at the intersection between neuroticism and extraversion. According to his theories, personality was primarily attributed to the sensitivity and reactivity of the nervous system, which he thought was mostly under genetic influence (33). Based on the extraversion-introversion and labile-stabile (representing the neuroticism scale) classification he divided personalities into 4 temperamental subtypes: the *melancholic, choleric, phlegmatic* and *sanguine* (34). Although not all of Eysenck's theories are considered up to date, they have contributed to later personality theories and for instance given arise to the Big Five traits extraversion and neuroticism (33).

A revised version of the EPI, **Eysenck Personality Inventory**, measures extraversion and neuroticism with 24 questions respectively. Additionally, it includes 9 questions to control for honesty (35). Generally, people tend to view high neuroticism as less desirable than low neuroticism. Therefore, it is a risk that the answers might reflect people's underlying values or their tendency to say "yes", rather than the measured personality trait (36, 37). In 2004 a study compared the original EPI to edited versions where the underlying connotations to the questions had been altered. For instance, the original question "Would you call yourself a nervous person?" was presented alternatively as "Would you call yourself a relaxed person?". According to this paper the test characteristics remained relatively similar. The control questions for dishonesty seemed to be good predictors for insincere answers (38).

There is evidence for that the traits presented in the five-factor model exist cross-culturally. However cultural differences may influence the interpretation of different personality tests (39). Cultural influences are also likely to affect how the individual traits are viewed and valued. Likewise people are likely to favor traits which support their current societal or cultural ideals (40). Therefore, some questionnaires have been standardized for specific study populations. For instance, the SSP, or the **Swedish Scales of Personality** are designed especially for the Scandinavian population. The cultural context should be kept in mind when interpreting the results of tests which are directed towards a certain group (41).

A benefit to the SSP is that it can be accessed free of charge (41). Likewise, the IPIP, the **International Personality Item Pool** has become an attractive source for psychometric testing as it contains a substantial collection of items that are available for free (42). In contrast, the NEO-PI is not publicly accessible. Despite having some of the most recognized psychometric properties, the NEO-PI cannot be utilized freely without payment. Additionally, the full version

of this test consists of well over 200 questions which may require a lot of time to complete (41). Different types of personality tests have been designed with specific goals in mind. For instance, the MIDI (**Midlife Development Inventory**) was created to achieve a quick personality assessment which could be especially practical when examining large populations (43). Another example is the BFI (**Big Five inventory**) which only takes the five basic traits in account without facet analysis. As a result it is quite short and easy to relate to (44).

2 Material and Methods

2.1 Study design

The purpose of this literature review is to examine if there is an association between the personality trait neuroticism and an increased risk of cardiovascular diseases (coronary heart disease and stroke). This paper summarizes cohort studies from the past 10 years. Cohort studies are proven to have a lower risk of bias than some other types of study designs, such as case-control studies. Cohort studies are therefore ranked higher up in the evidence hierarchy (45). There are multiple benefits to a cohort study design, such as greater control over the relation between the exposure and the outcome in comparison to cross-sectional analyses. Despite often requiring more time and resources to conduct, cohort studies offer more reliable information on causality in contrast to studies where baseline information is collected retrospectively (46).

Additionally, this review utilizes some of the principles described in the PRISMA model. This model stands for “the Preferred Reporting Items for Systematic reviews and Meta-Analyses” and it provides a systematic approach to summarizing information from the literature (47). Although this review covers many but not all the 27 items described in the checklist, it has adapted a more narrative point of reference rather than statistical. Therefore, it may not be classified as a fully systematic review. Despite this limitation, this study focuses on presenting the methodology and findings in a structured and open manner. The literature was selected with defined inclusion and exclusion criteria from recognized medical and psychological databases. The goal was to summarize papers with the highest quality of evidence available from the past 10 years and provide a transparent interpretation of potential biases.

Only randomized controlled trials, systematic reviews and meta-analyses are ranked above cohort studies in the evidence pyramid (45). Therefore, the focus of this paper is summarizing studies with a cohort study design. With the current research question in mind, randomized

controlled trials are not relevant as it is not possible to assign personality traits to people as an intervention. However, review articles of cohort studies are also included, given that they meet the eligibility criteria. To my knowledge, there are no meta-analyses conducted on this specific research question.

2.2 Eligibility criteria

The focus of this paper is to review relevant medical literature from the past decade to assess whether there is an association between high neuroticism and cardiovascular disease. More specifically, to assess whether high neuroticism causes an increased risk of getting coronary heart disease and/or stroke. In some studies, the number of CVDs is reported based on data from death registers. However, not all new cases of stroke or heart disease are fatal and CVD related mortality has been declining during the recent decades (8). Therefore, papers which strictly examine the association between neuroticism and CVD related mortality are excluded from the analysis. This report includes only papers which either use incident non-fatal CVDs or incident non-fatal and fatal CVDs as the end outcome.

Likewise, articles which do not precisely answer the research question "is high neuroticism a potential risk factor for cardiovascular diseases?" are excluded. Examples include papers which analyze the effect of neuroticism on the specific risk factors of CVD. For instance, papers which study the impact of high neuroticism on cholesterol levels are excluded. Similarly, studies which look at the effects of neuroticism on the prognosis of cardiovascular disease are not relevant for this report. Also, papers which study the effects of Big Five personality traits in the aftermath of a cardiovascular event are not included. Examples include studies that analyze the risk of post-stroke depression in the light of neuroticism.

Additional eligibility criteria include restrictions in study design, publication date and population group. The foundation for including only papers with a cohort study design is based on the pyramid of evidence and explained more closely under "2.1 Study design" (45). The purpose of this review is to summarize recent evidence from the past decade on the research of the link between personality and cardiovascular disease. Therefore, studies published before 2013 are excluded from the report. In order to ensure sufficient statistical power, only cohort studies with over 1000 participants are included in the final analysis. All included papers are required to have a full-text available in a Scandinavian or English language. The articles

included in the analysis are gathered from relevant medical and psychological databases. In this report MedLine and APA PsycNet.

2.3 Search strategy

All literature included in the final analysis was sourced from databases MedLine (Ovid) and APA PsycNet. Two different literature searches were conducted on two separate occasion, one search in each database. The literature searches are presented in detail down below. Different search terms and filters were used in the respective databases due to the variance in their contents. APA PsycNet is operated by the American Psychological Association and it does not cover as extensive somatic biomedical information as MedLine. Therefore, the literature search made in APA PsycNet did not pick up as many irrelevant results as the literature search in MedLine. The search made in MedLine required more specifying search terms and filters to narrow down the number of hits to be able to find the relevant studies. The undersigned screened and sorted the search results manually according to the inclusion and exclusion criteria.

The first literature search was made 22.08.2023 in MedLine (Ovid) (accessed through the Arctic University of Norway). The search was constructed based on the main exposure (neuroticism) and outcome (cardiovascular diseases) of interest in mind. I initially started with the combination of “neuroticism” and “cardiovascular disease”. Synonymous search words for “cardiovascular disease” were added: “coronary disease”,” coronary heart disease” and “stroke”. Meanwhile, to my knowledge “neuroticism”, at least when referred to as a personality trait in the five-factor model, does not have any precise synonyms. It could perhaps be described as “lability” or “nervousness”, but according to my observation such terms were not precise enough to target specifically studies on the personality trait neuroticism. Likewise, replacing neuroticism with terms like “personality traits” or “Big Five” rather just provided an abundance of information irrelevant to the research question.

The search terms were also supplied with filters. “Neuroticism”, “cardiovascular disease”, “coronary disease” and “stroke” were used as MeSH terms (MeSH, explode), including all subheadings. Additionally, all search words were used as keywords. Furthermore, these terms were also coded to target papers with the search words in their titles. Despite the add-ons, the search results still provided way too many irrelevant papers for manual screening. I noticed that the search picked up papers which studied some aspect of personality and cardiovascular

disease but not the risk of getting cardiovascular disease. The addition of a third search term describing the potential relationship between the exposure and the outcome remarkably increased the proportion of relevant studies. The addition of "risk factors" as a MeSH term (MeSH, explode) and keyword, as well as the term "risk" as a title search narrowed down the proportion of papers which were irrelevant to the research question.

Consequently, the final literature search in MedLine gave 123 hits (22.08.2023). The search is presented in Figure 2.

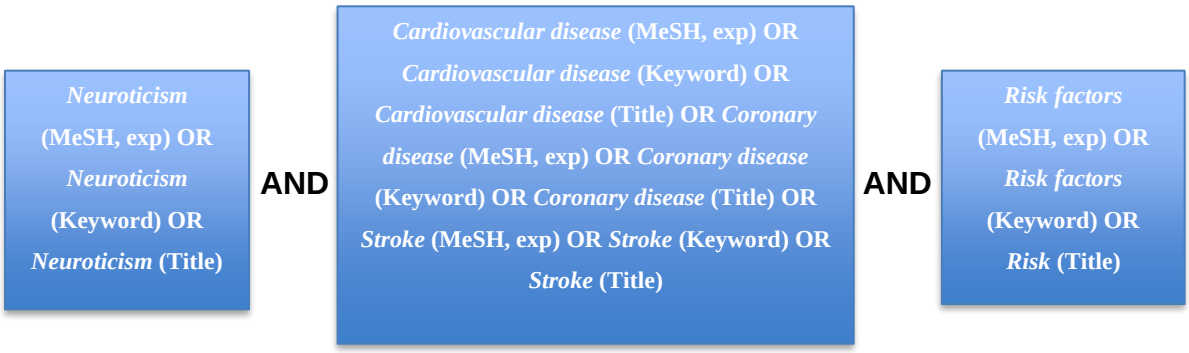

Figure 2: *Illustration of the MedLine literature search*

In January 2024, an additional literature search was conducted in another database. The goal was to detect studies that were not detected earlier in the original MedLine literature search. The second literature search was performed on 26.01.2024 in the APA PsycNet database through https://psycnet.apa.org/search/advanced. I quickly noticed that when typing in typical search terms there were not nearly as many hits available as in the previous database. I initially started with a similar search as in the previous literature search, but as it did not provide too many search results, I started to widen the search by removing the filters. I also removed the addition of "risk factors" as it was no longer necessary. The final literature search consisted of the word "cardiovascular disease" alongside alternative search terms ("coronary disease", "myocardial infarction", "stroke", "heart disease") and "neuroticism".

Consequently, the final literature search in APA PsycNet gave 18 journal articles (26.01.2024). The search is presented in Figure 3.

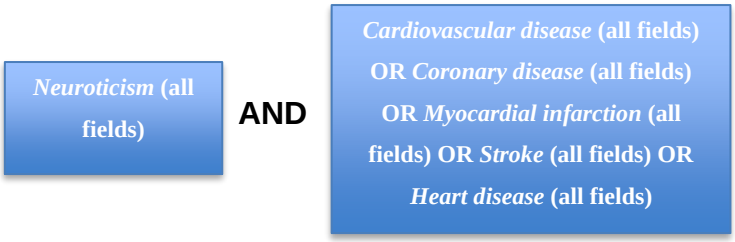

Figure 3: *Illustration of the APA PsycNet literature search*

2.4 Selection process

The literature searches in MedLine and PsycNet gave in total 141 hits. 2 duplicates were detected. After the removal of the duplicates, all search results underwent a manual screening process where initially all abstracts were screened (n=139). The first criterion for exclusion was not answering the research question. 77 papers were excluded for this reason. Out of the excluded articles, 11 were excluded due to using only mortality as the end outcome. Additionally, at least 20 papers were excluded due to focusing on the risk of psychological complications after a cardiovascular event. The remaining papers that were excluded based on the research question were either completely irrelevant to the research question or did not answer it precisely enough. For example, articles that studied the effects of personality on cholesterol levels or other risk factors of CVD.

The excluded articles most likely fulfill multiple exclusion criteria. However, once encountering on one criterion for exclusion, the article was no longer screened for additional exclusion criteria. 27 papers were excluded based on the study design. Papers ranking below cohort studies in the evidence pyramid, such as cross-sectional analyses and editorials, were removed. 9 studies were excluded for including less than 1000 participants. Articles published in non-Scandinavian or non-English languages were excluded. These included papers in German, Polish and French (n=4). Additionally, 2 papers did not have a full-text available and were also not included in the final analysis. Finally, 10 papers were excluded for being published before 2013.

Consequently, **10 studies** from the literature search were included in the finals analysis (MedLine n = 9, APA PsycNet n = 1). The articles are presented in table 2.

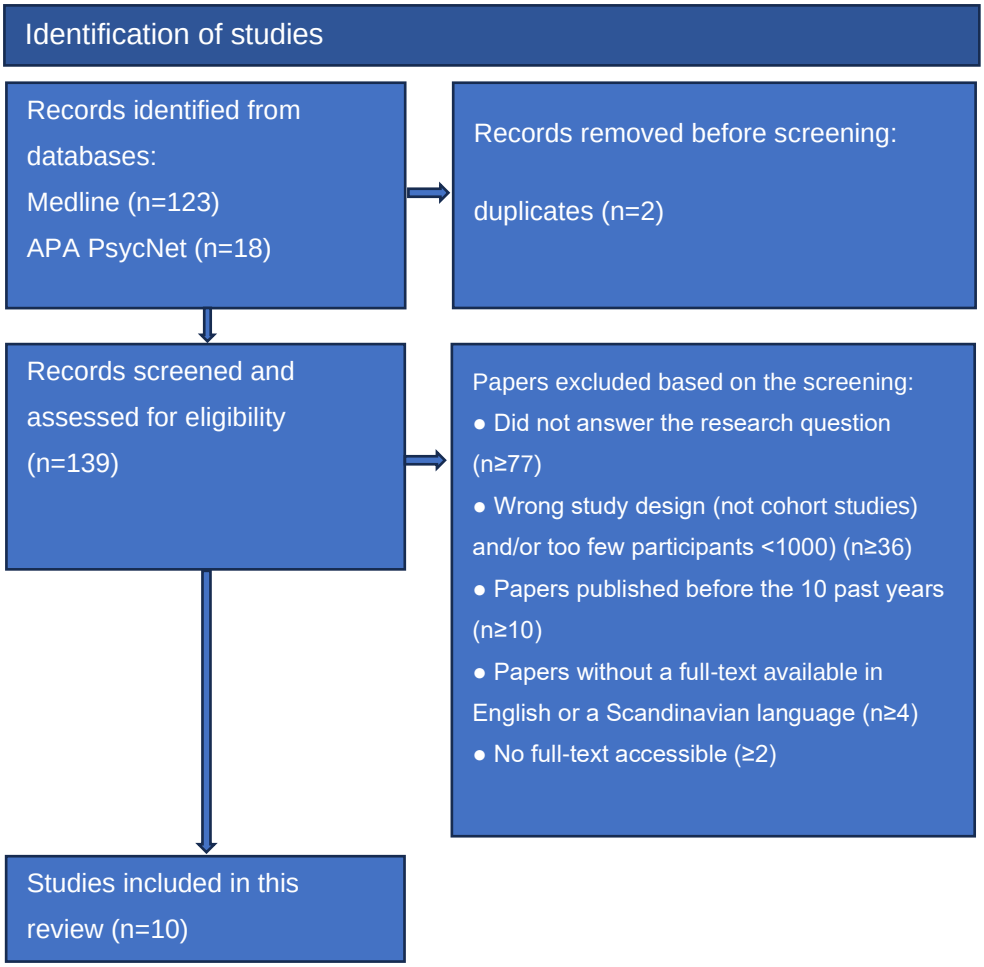

Figure 4: *Illustration of the literature search and selection process*

2.5 Evidence assessment

All articles included from the literature search are presented in table 2. The table form presentation comprises some of the distinctive characteristics of the individual studies. This includes authors, population-sizes, follow-up times and a short description of the construction of the studies including main findings. Additionally, each study has been assigned an evidence grade inspired by GRADE evaluation principles (48). The PRISMA guidelines cite that the assessment of the evidence level as well as a description of potential errors play a crucial part in the methodology of summarizing reviews (47). In this review I attempted to meet several of these criteria through grading. The GRADE evaluation method is recognized for its systematic approach towards assessing the level of evidence in studies. This method is based on the collective evaluation of defined factors in study construction.

The starting point is defined by the type of study in question. A randomized controlled trial will be characterized by a higher evidence degree already from the start, in comparison to an

observational study. After the initial assessment of study design, the study is rated according to a checklist in relation to 8 aspects. These points will help to determine which quality of evidence the findings represent (A-D). Despite its systematic approach to evidence assessment, GRADE evaluation is still affected to a certain degree by subjectivity and will arguably also reflect the experience level of the evaluator (48). All the grades assigned in this paper are based on my subjective evaluations and are open to interpretation. To ensure transparency, the specific criteria for downgrading, or alternatively upgrading, the evidence degree are presented in table 3.

Beside the evaluation of study design, additional points of reference include “risk of bias”, “consistency”, “directness”, “precision” and “risk of reporting bias”. The nature of the intervention proposed some challenges during the assessment of the “risk of bias” point. According to the GRADE handbook, a lot of attention should be given to the process of randomization and blinding when analyzing the differences in groups (49). However, due to the current research question in mind it is rather challenging to design any assigned interventions to mimic the effects of neuroticism precisely enough. Despite a longitudinal design, the observational nature of the studies included is a noteworthy limitation. It is suggested that studies with an observational character should already at the beginning be classified in the “low evidence” category.

Due to this obvious limitation, most of the studies have received either a “low” (C) or “very low” (D) quality grade. Factors which downgrade the level of evidence include limitations in relation to the risk of several different types of biases, as well as inconsistencies, indirectness, or imprecision in the study construction, conduction or presentation. The consistency of the results was evaluated against the other studies included in the literature search. The use of surrogate outcomes was rather successfully eradicated already during the selection process, although some of the outcomes were self-reported. The evidence level can also be upgraded in accordance with certain criteria. For example, a dose-response effect between the exposure and the outcome may in some cases upgrade the quality of evidence. The more detailed principles in GRADE are described elsewhere (48, 49).

3 Results

A total of 10 research papers met the inclusion criteria and were included in this review. For an overview of the studies, please view Table 2. In total, 7 out of 10 papers found a positive

association between cardiovascular diseases and high neuroticism. All studies answered the research question “does neuroticism increase the risk of getting cardiovascular diseases?”. Two studies defined cardiovascular diseases as a pooled outcome consisting of several different conditions (6, 50), while 6 studies analyzed separately the outcome of stroke (51-56). Additionally, 5 studies analyzed separately the outcome of myocardial infarction or coronary heart disease (52, 53, 56-58). In total, 4 out of 10 studies focused specifically on non-fatal incidents of CVD. The comparative hazard ratios for MI/CHD are displayed in table 1.

3.1 Presentation of the studies

Dahlen et al., 2022

The largest study which focused on the link between neuroticism and myocardial infarction was published in 2022. The UK Biobank is a biomedical database that contains information on approximately 500,000 subjects. Dahlen et al. analyzed data from 460,865 UK Biobank participants for a 7-year follow-up period. 54,9% of the participants were women. The mean age was 56,3 for men and 56,6 for women. Neuroticism was measured with the EPI-N, or the Eysenck Personality Inventory questionnaire. This questionnaire comprises of 12 questions with scores ranging from 0-12. The end outcome was defined as non-fatal and fatal myocardial infarction. Data on the studied outcome was collected from hospital records, death registers and patient reports.

During follow-up, 4,852 new cases of MI (myocardial infarction) occurred. The results were adjusted for traditional non-modifiable and modifiable risk factors. Smoking, hypertension, physical activity, diabetes, weight, alcohol intake, age, sex and ethnicity were used as confounders. Meanwhile, cholesterol levels, dietary intake, and family history of MI were not considered in the analyses. The authors discovered that neuroticism was positively associated with incident myocardial infarction, HR 1.03 (CI 1.02-1.04). Interestingly, the trait nervousness, constructed based on 5 questions proposed an even larger risk of MI, HR 1.07 (CI 1.04-1.09) (58)

The authors also discovered a gender difference. Sex is a non-modifiable risk factor for cardiovascular disease. Generally, men get myocardial infarction and stroke at a younger age than women. Additionally, males more often than females suffer fatal consequences (8). In their study, Dahlen et al. noted that women high in neuroticism were more vulnerable towards developing MI, HR 1.05 (CI 1.03-1.07) in comparison to men, HR 1.02 (CI 1.01-1.03). The

difference was especially notable for the characteristic of nervousness in women HR 1.13 (CI 1.08 – 1.19) when compared to men HR 1.05 (CI 1.02-1.08) (58).

Li et al., 2022

Li et al. discovered a somewhat similar observation. Women faced an increased risk of CVDs due to poor mental health in comparison to men. The authors followed up 339,616 participants (45,1% women) aged 40-69 from the UK Biobank for 11.3 years. The main outcome was CVD, including coronary heart disease and stroke. Data on the outcomes was collected from medical records. The results were adjusted for all traditional cardiovascular risk factors. The main goal of this study was to analyze the relationship between mental health and risk of CVD. One of the factors included in the analysis was neuroticism. Mental health was assessed using the questionnaires PHQ-2 (patient health questionnaire 2-item), GAD-2 (generalized anxiety disorder 2-item questionnaire), EPI-Q12 (Eysenck Personality Inventory questionnaire) and loneliness (yes/no). Each participant was assigned a score based on the sum of the answers. A score of 6 or more in the EPI-Q12 was defined as high neuroticism.

During follow-up 22,688 incidents of CVD occurred (18,460 coronary heart disease, 5070 stroke). The participants were split into 5 categories based on their mental health score. Those in the highest category facing the most mental health issues also had the highest risk of all outcomes. In fact, the risk increased in a dose-response manner. Those with the worst mental health had a hazard ratio of 1.56 (CI 1.47-1.65) for CVD in comparison to the control group (score 0). The risk was increased for both CHD (coronary heart disease), HR 1.61 (CI 1.51-1.72) and stroke HR 1.44 (CI 1.25-1.67). Affective symptoms, including depression and anxiety, were the most important contributors to the increased risk. Neuroticism also contributed to an increased risk of CHD HR 1.22 (CI 1.18-1.26) but the effect was more moderate than the 3 other variables. Yet, the association between neuroticism and CHD remained positive HR 1.09 (CI 1.05-1.13) even after adjusting for affective symptoms. Neuroticism was not associated with an increased stroke risk (52).

Sun et al., 2022

Sun et al. followed up 126,255 subjects in the UK Biobank for 11.5 years. The goal was to study the relationship between psychological health and the risk of getting cardiovascular diseases. One of the components included in the assessment of the participants' psychological wellbeing status was neuroticism. The authors argue that the components which constitute good

psychological health are often tightly knit together and therefore it could make sense to rather analyze the effects of the sum of these components than to focus on the individual factors. Thus, "psychological wellbeing" was operationalized as the calculated score of four different psychological aspects of health: "happiness", "depression", "life satisfaction" and "neuroticism".

Each participant was assigned a score from 0-4 representing their overall psychological wellbeing status. The participants were then divided into low, intermediate and high-risk groups ranging from worst to best mental wellbeing status and the results were analyzed accordingly. It was also conducted sub-analyses of the impact of the individual traits which constructed this score and their influence on cardiovascular health risks. Neuroticism score was based on the EPI-N questionnaire and scores ranged from 0-12. Meanwhile, the outcome, cardiovascular disease, was defined as coronary heart disease, stroke, or heart failure. The participants were free from these types of CVD at baseline. Information on the development of cardiovascular diseases was gathered from medical records and death registers.

During follow-up 10,815 incidents of CVD occurred. Data on traditional risk factors (smoking, hypertension, cholesterol, diet, physical activity, diabetes, weight, alcohol intake, age, gender, ethnicity and socioeconomic status) was collected from the participants. Antipsychotic medication use, sleep characteristics and C-reactive protein were also considered. Data on family history of cardiovascular disease was not provided, but a part of the study population was subjected to a sub-analysis of the impact of high-risk single nucleotide polymorphisms. High neuroticism was found to be a risk factor for CHD, HR 1.14 (CI 1.07–1.21) but there was not an association between neuroticism and stroke or HF (heart failure). Alongside neuroticism the authors also included sub-analyses of the impact of the other traits included in the psychological health score. "Depression" and poor "life satisfaction" scores carried an even stronger association to CHD than neuroticism (53).

Almas et al., 2017

Similar studies have previously been conducted among smaller study populations. In 2017 Almas et al. studied the association between neuroticism, depression and cardiovascular disease among 10,443 participants (42,3% men) (56). The participants were selected from the PART cohort study, which stands for "Psykisk hälsa, arbete och relationer" or in English, freely translated into "Mental health, work and relationships". In this cohort, participants were

recruited from the Swedish capital. The authors had previously conducted a study where they examined if depression caused an increased risk of CVD. Their earlier conclusion was that depression is a cardiovascular risk factor, HR 1.9 (CI 1.4-2.5) when adjusting for age and sex (59). The purpose of the current study was to account for the role of neuroticism when it comes to cardiovascular risk of depression.

During follow-up (2001-2014) 537 participants developed cardiovascular disease. The information on the outcomes was collected from patients' medical records. Out of this number 46% represented new incidents of stroke. The remaining amount reflected the number of people who developed heart disease. Heart disease was defined as either coronary disease or heart disease attributed to chronic blood pressure elevation. The SSP, or the Swedish Scale of Personality was used to measure the level of neuroticism in the participants. Depression score was calculated based on the MDI, the Major Depression Inventory. The patients who developed CVD were divided into groups based on depression status (yes/no) and neuroticism level (high/low).

According to this paper, those who were high in neuroticism but did not have depression had a 1.4 (CI 1.1-1.8) hazard ratio for cardiovascular disease. According to sub-analyses, the corresponding hazard ratios were 1.7 (CI 1.2-2.3) for heart disease and 1.3 (CI 1.0-2.0) for stroke. These numbers were adjusted for traditional risk factors including smoking, hypertension, physical activity, diabetes, weight, alcohol consumption, age, gender and socioeconomic status. When neuroticism occurred together with depression the risk of cardiovascular disease was higher than with neuroticism or depression alone (56).

Morton et al., 2018

In 2018, Morton et al. studied the potential association between personality and MI. Additionally, the goal was to assess the relationship between adverse childhood experiences and the composition of personality traits (57). Personality development is thought to be a consequence of environmental, social as well as genetic factors. Yet, the proportion to which the individual factors account for is debated (40). Genetic risk can be approximated with the help of twin studies. Some researchers suggest that genetic influence may be responsible for around 30-60% (60). These results indicate that the social and environmental impact is still quite remarkable. In the 2018 study, the authors wanted to assess how different kinds of adverse

childhood events contribute to unfavorable health outcomes in adulthood, while accounting for personality.

In this study, 3,012 participants were followed up from baseline (1995-1996) to the end of the follow up period (2004-2006). Data was recruited from the MIDUS study, which stands for the "Midlife in the United States" study (57). In the longitudinal study, personality assessment was conducted with the MIDI (Midlife Development Inventory), which has been specifically created to achieve a quick personality analysis of large populations (61). Adverse childhood experiences were analyzed with a question form on the participants' early experiences in relation to different disadvantageous events. The form included questions on physical and emotional abuse, parental education level and civil status, experiences of losing a parental figure, economic challenges and health struggles. The outcome was defined as non-fatal incidents of MI which was based on patient reports.

Morton et al. discovered an association between neuroticism and MI, HR 1.441 (CI 1.017-2.040). Additionally, the self-reported adverse childhood experiences were associated with an increased risk of MI, HR 1.058 (CI 0.982-1.138). Likewise, the disadvantageous childhood events were also linked to the personality trait neuroticism. The authors suggest that the etiology of high neuroticism may in some cases be traced back to unfortunate early life experiences. Therefore, they suggest that it may indeed be childhood misfortune that contributes to increased neuroticism, which is linked with an increased risk of cardiovascular disease (57).

van Zutphen et al., 2023

The relationship between affective disorders and cardiovascular risk has been widely studied in the past. A meta-analysis published in 2017 concluded that depressed patients face an increased risk of cardiovascular disease. Likewise, having a severe mental illness increased the risk of both prevalent and incident cardiovascular disease, as well as CVD related mortality (62). In a 2023 study, van Zutphen et al. studied the association between depression and cardiovascular disease. The purpose of the study was to evaluate which additional characteristics play a role in this equation. Big Five personality traits were included in the analyses as potential "depression-related characteristics".

This study included 1028 participants with a mean age of 44,6 years. Most of the participants were female (68,2%). The data was collected from two longitudinal studies on depression in the Netherlands. These were the NESDA ("Netherlands study of Depression and Anxiety") and

the NESDO ("The Netherlands study of depression in older persons" (sic)) studies. Personality traits including neuroticism were recorded with the NEO-FFI. High neuroticism was defined as a score 32 or more, which was the median value. The outcome, cardiovascular disease, was based on patient reports. The subjects were also questioned on medication use. It was not performed sub-analyses on the risk in relation to different kinds of cardiovascular disease, but CVD was rather defined as a pooled outcome with the precondition of atherosclerotic origin.

During approximately 5,4 years of follow-up, 131 participants developed cardiovascular disease. The authors did not detect any significant association in relation to neuroticism. However, the risk of getting a cardiovascular disease increased with affective disease severity. Severe depression, HR 2.12 (CI 1.30–3.48) and severe anxiety, HR 2.63 (CI 1.42–4.87) were the only associated characteristics in this study when the results were adjusted for additional risk factors (smoking, hypertension, cholesterol, physical activity, weight, alcohol consumption, age, gender and education level) (50).

Luo et al., 2022

In 2022 Luo et al. investigated the association between personality and several different health outcomes. The authors utilized data from three different longitudinal studies in their analyses. Only one of the studies included information on cardiovascular risk. This study is the SATSA study which stands for "The Swedish Adoption/Twin Study on Aging". Information on individual Big Five personality traits was gathered using the Eysenck Personality Inventory. The outcome was defined as a pooled group consisting of several different self-reported cardiovascular conditions. Sub-analyses of the specific diseases were not conducted. The participants in the SATSA study were followed for 14 years. After controlling for age and sex, the authors concluded that high neuroticism was associated with an increased risk of CVD, r 0.22 (CI 0.13-0.30).

Personality data was collected 6 times throughout the follow-up period. Luo et al. point out that when it comes to analyzing the effects of personality on somatic conditions one must take in account the potential for changes in personality over time. Personality is defined as a "relatively stable set of characters". However, the authors claim that different experiences, including adverse health outcomes, throughout life could have an impact on personality development. Therefore, Luo et al. used a the RI-CL, Random Intercepts Cross-Lagged Panel Model as well as CT-model, Continuous-Time-model, to analyze the potentially reciprocal relationship

between these variables over time. Luo et al. found a positive link between neuroticism and CVD in the study population, but personality changes throughout lifetime did not significantly impact this risk (6).

de Ruijter et al., 2022

The link between personality and stroke risk was investigated in a 2022 UK Biobank study. Data was analyzed from 461,168 participants (55% women, mean age 56-57 years), making this the largest cohort included in this review. Information on baseline characteristics was collected from the subjects and the follow-up time was 7 years. Neuroticism was assessed with the EPI-Q12 with scores ranging from 0-12. Meanwhile, information on the outcome of stroke was gathered from medical records, the participants themselves as well as information from death registers. In addition to cross-sectional prevalence analyses, the authors specifically focused on recording non-fatal stroke incidents throughout the follow-up period.

In total 3312 non-fatal stroke incidents occurred in the longitudinal part of this study. The results were adjusted for characteristic cardiovascular risk factors including smoking, hypertension, physical activity, diabetes, weight, alcohol consumption, age, gender, ethnicity and socioeconomic status. Information on cholesterol levels, dietary habits or family history of cardiovascular disease was not provided. The authors did not find any significant association between neuroticism and stroke risk. Additionally, the characteristic of nervousness was tested against the same hypothesis. Overall, the results remained insignificant in the multivariate models (54).

Henderson et al., 2013

Henderson et al. conducted a study on the link between psychosocial affliction and cerebrovascular events. All participants were over 65 years old. They were recruited from the CHAP study, which stands for the “Chicago Health and Aging Project” study. The authors included data from 4120 participants in the mortality study (61,8% women, mean age 77,1). Meanwhile, 2649 individuals were included in the analyses for incident stroke. The exposure was a mental affliction score that comprised of 4 different factors, including a neuroticism assessment. Neuroticism level was documented with the NEO Five-Factor Inventory. Data on the outcome of interest was defined as stroke, regardless of hemorrhagic or ischemic origin. Information on the outcome was based on patients’ medical records.

The subjects were followed up for 6 years. During the follow-up period 452 stroke incidents occurred. The authors could not detect any significant association between neuroticism and cerebrovascular events after adjusting for confounding factors (smoking, hypertension, diabetes, use of cholesterol medication, physical activity, diabetes, weight, age, gender ethnicity and socioeconomic status). However, the collective amount of distress was positively associated with an increased risk for hemorrhagic stroke, HR 1.70 (CI 1.28–2.25). In addition to neuroticism, the distress score took in account depression, stress and lack of life-satisfaction (51).

Stephan et al., 2023

On the other hand, Stephan et al. reviewed data from multiple longitudinal studies with the conclusion that neuroticism is associated with increased stroke risk. This study published in 2023 includes data from 58,105 participants, aged 16-104. The study population consisted of participants in 6 different longitudinal studies with American, British or Dutch origin: the MIDUS (Midlife in the United States), HRS (Health and Retirement Study), NHATS (National Health and Aging Trends Study), WLS (Wisconsin Longitudinal Study), LISS (Longitudinal Internet Studies for the Social Sciences) and US (Understanding Society) studies. Personality traits including neuroticism were assessed with the Midlife Development Inventory (MIDUS, HRS, NHATS), the Big Five Inventory (WLS, US) and the International Personality Item Pool (LISS).

The cohorts were followed up for 7-20 years. During this period, 2313 stroke incidents occurred. The authors focused on non-fatal incidents which were based on self-reported data. The results were adjusted for traditional risk cardiovascular risk factors including smoking, hypertension, physical activity, diabetes, weight, age, gender, ethnicity (in 4/6 cohorts) and socioeconomic status. Data on cholesterol levels or use of lipid lowering drugs, dietary intake, alcohol consumption and family history of cardiovascular disease was not reported. In this study there was a positive association between neuroticism and stroke risk HR 1.13 (CI 1.05-1.21). (55)

	The association between high neuroticism and risk of heart disease:
Almas et al. 2017	HR 1.7 (CI 1.2-2.3) (CHD/hypertensive heart disease)
Morton et al. 2018	HR 1.44 (CI 1.02-2.04) (MI)
Li et al. 2022	HR 1.09 (CI 1.05-1.13) (CHD)
Sun et al. 2022	HR 1.14 (CI 1.07–1.21) (CHD) HR 1.04 (CI 0.93–1.17) (HF)
Dahlen et al. 2022	HR 1.03 (CI 1.02-1.04) (MI)

Table 1: *Comparison of Hazard ratios for myocardial infarction/coronary heart disease. This table shows the association between high neuroticism and the risk of developing heart disease (MI/CHD/hypertensive heart disease) in the different studies included.*

3.2 Other Big Five personality traits

This study does not focus on the remaining Big Five personality traits other than neuroticism. Therefore, other personality traits have not been taken in account in the literature search. However, it is worth mentioning some of the results in the major studies regarding the remaining traits. De Ruijter et al. found a reverse association between conscientiousness, as well as extroversion and stroke risk. Similarly, Dahlen et al. noted a cardioprotective effect of traits representing conscientiousness, HR 0.88 (CI 0.85.-0.92) and extraversion, HR 0.90 (CI 0.87-0.93) in relation to risk of MI. In relation to stroke risk, Stephan et al. also made a similar observation regarding conscientiousness, HR 0.92 (CI 0.87–0.98), but not extraversion. A plausible explanation could be that highly conscientious individuals may be more likely to adhere to a healthy lifestyle. Also, it is likely that high conscientiousness would be accompanied by better compliance in a clinical setting (63).

4 Discussion

4.1 Coronary heart disease

The research on neuroticism and risk of coronary heart disease pointed mostly unambiguously towards a small yet significant association. The comparison of hazard ratios for CHD and/or MI are presented in table 1. The ratios are not entirely analogous to each other as heart disease

was defined variously in the papers. Almas et al. included also hypertensive heart disease into the risk score whereas others defined it with more strict terms (56). The HR's for CHD or MI ranged between 1.03 (CI 1.02-1.04) and 1.14 (CI 1.07–1.21) in the three largest study samples included (Li (52), Sun (53), Dahlen (58)). Meanwhile, the two remaining smaller studies presented with larger confidence intervals.

Although the results indicate a link between personality and heart disease, it is still noteworthy that the evidence does not undermine the influence of the traditional cardiovascular risk factors. For instance, Dahlen et al. point out that out of all covariates, diabetes had the largest impact, increasing the likelihood of having an MI with up to five times. In the discussion they also shed light upon additional important variables, specifically male gender and smoking, both of which carried a stronger association to MI risk than high neuroticism (58). Likewise, affective diseases have been connected to increased cardiovascular risk. According to a meta-analysis published in 2023 depression attributed to an increased risk of MI, HR 1.28 (CI 1.14-1.45) (64). As neuroticism is associated with psychopathology (23), it is not entirely possible to exclude the effects of such confounding factor.

However, some articles also took this into account. For instance, Li et al. found an association between high neuroticism and increased risk of CHD, HR 1.22 (CI 1.18-1.26). The corresponding numbers were HR 1.44 (CI 1.38-1.51) for anxiety and HR 1.40 (CI 1.32-1.48) for depression. The authors took in account that it is likely that there was an overlap among those high in neuroticism (N=4461) and for instance those high in anxiety (N= 2239) who developed CHD. Therefore, additional analyses were performed where the numbers were adjusted for anxiety, depression, and loneliness. Contrary to what could have been expected, the association between neuroticism and CHD remained positive, HR 1.09 (CI 1.05-1.13) even when accounting for a wide range of traditional risk indicators (52).

Similarly, Almas et al. (2017) performed separate analyses for the effects of neuroticism and depression respectively on cardiovascular diseases. Additionally, they investigated the summed effect of both conditions. In the results, the authors present that increased neuroticism had a positive association with CVD risk (OR 1.2 (95% CI 1.1–1.3) (56). However, these numbers cannot be found in table-form. In the graphic presentation it appears as if the CVD risk was HR 1.4 (CI 1.1-1.8) for non-depressed individuals and HR 1.8 (CI 1.2-2.4) with simultaneous depression (56). In the introduction of their study, the authors also referred to their earlier research in relation to depression as a potential risk factor for cardiovascular disease. However,

the hazard ratio that the authors present was not subjected to the fully adjusted multivariate analysis, which had ultimately reduced the effect of the association in the original study (59).

4.2 Cardiovascular disease as a pooled outcome

Luo et al. analyzed data from three cohorts, one of which analyzed specifically the link between neuroticism and CVD. The focus of the study was to assess the link between personality and several different kinds of somatic outcomes. Despite detecting a positive association between neuroticism and adverse cardiovascular outcomes, the methodology of the study remains a bit unclear to the undersigned. For instance, in relation to the analysis of cardiovascular risk, it is not mentioned anything about the possibility of co-existing diabetes. While, age and gender are mentioned as confounding variables the consideration of extended risk evaluation needs some elaboration (6).

van Zutphen et al. also defined the outcome as a pooled category. The authors did not find any significant association between high neuroticism and CVD, HR 1.31 (CI 0.90–1.90). However, out of all studies included in this report, this study had the smallest number of participants (N=1028). However, the percentage of participants who developed cardiovascular disease was quite high (~13%). There was a link between severe affective disorders and CVD. This result is consistent with other studies included from the literature search; that affective disorders carry a larger risk of coronary heart disease than neuroticism does (52, 53). Therefore, it could be that the sample size was not large enough to produce sufficient statistical power nor to be able to distinguish between subcategories of CVD.

The authors acknowledged this and referred to the fact that the associations would have been too weak due to a small population if further divided into disease-specific categories. For instance, both Li et al. and Sun et al. studied the effect of neuroticism on heart disease as well as on stroke, but only found a link between the former of the two outcomes (52, 53). This could indicate that the risk factors for heart disease and stroke are not entirely the same, despite overlapping to a very significant degree. One could also hypothesize that increased neuroticism could be protective in case the individuals would feel increased health related anxiety and be more liable to follow a healthy lifestyle. However, at least for heart disease this does not appear to be the case (50). Additionally, both van Zutphen et al. and Luo et al. based the outcomes on self-reported data (6, 50).

4.3 Stroke

Research on personality and stroke risk was not as unambiguous. Six studies either focused separately on stroke as the main outcome or performed sub-analyses of stroke incidence in the study population. Most of the studies did not detect any significant association between high neuroticism and increased stroke risk or the association was mitigated in the fully adjusted models. The three largest studies included large study populations with 126,255-461,168 participants and did not find any significant association (52-54). In the largest study, only the cross-sectional but not the longitudinal analyses indicated an association (54). Meanwhile, Stephan et al. found a positive association despite having a significantly smaller study population consisting of 58 105 participants in 6 different longitudinal studies (55). Despite a smaller study population, they found a relatively higher stroke incidence of 4.0%. The corresponding numbers were 0,1% for de Ruijter et al., 1,5% for Li et al. and 1,7% for Sun et al.. Almas et al. were the only other authors that besides Stephan et al. found an association between neuroticism and stroke risk, HR 1.3 (CI 1.0-2.0 (56).

Generally, there was an overweight of men and older people among the participants who developed stroke. As presented earlier, Stephan et al. used data from 6 longitudinal studies (the MIDUS, HRS, US, WLS, NHATS and LISS studies). The percentage of women varied from 54 to 59% across all samples. The participants had a quite large age gap between 16-104 years. The two studies with a percentage-wise highest stroke incidence were the NHATS (*National Health and Aging Trends Study*) and the HRS (*Health and Retirement Study*) studies with a 10% incidence rate. These studies included the oldest participants with a mean age of 79 and 68 respectively (55). Meanwhile, de Ruijter et al., Li et al. and Sun et al. had overall younger study populations with the average age 56 years (55,2% women), 56 years (45,1% female) and 55-57 years (47-66% women across samples) respectively (52-54).

While the three largest studies did not find an association between high neuroticism and increased stroke risk, it is notable that they all used data from the UK Biobank. The UK Biobank contains information on 500 000 subjects. This indicates an overlap among the 126,255 to 462,268 participants included in the three study populations. The authors selected participants based on differences in criteria related to stroke status. De Ruijter et al. also included patients with previous stroke (N=6793) in the study population (N=461,168) (54). Meanwhile, Li et al. and Sun et al. excluded patients with prevalent cardiovascular disease ending up with smaller study populations (52, 53). Likewise, Stephan et al. also excluded patients with previous stroke (55). Previous stroke increases the risk of a new cerebral event up to around 20-30% (65). However, in this review it does not explain the contradictory results.

Stephan et al. did not adjust for some potentially important confounding factors like alcohol intake (55). A high consumption of alcohol (100g/day) may increase the risk of at least hemorrhagic stroke with RR 4,7 (CI 3,35-6,59) according to the Norwegian Institute of Public Health. Even smaller amounts of alcoholic beverages could influence the risk of developing risk factors for stroke, such as hypertension and atrial fibrillation (66). It is also possible that personality is associated with drinking habits. In cross-sectional analyses neuroticism has been linked to increased alcohol consumption (67). Therefore, it is not possible to exclude whether the effects of this study reflect an association between neuroticism and stroke risk or the effects of a confounding variable. Additionally, the authors did not provide information on the participants cholesterol levels or use of lipid lowering drugs and dietary habits (55).

Lastly, all of the cohort studies which were analyzed in the review by Stephan et al. utilized self-reported data as the outcome. The question of stroke incidence was proposed differently in the separate cohort studies. For instance, in one of the cohorts, the patients were among other questions asked if they had had a "disease affecting the blood vessels in the brain". It is uncertain whether some patients could possibly interpret this question in ways other than strictly "stroke" (55). Perhaps some patients could also have replied "yes" to having had another neurological condition. On the other hand, none of the other studies on stroke risk used strictly self-reported data. For example, de Ruijter et al. took the patients reports in consideration but also used data from medical and death records (54).

4.4 Possible underlying mechanisms

This literature review found a positive association between the personality trait neuroticism and myocardial infarction or coronary heart disease. One potential underlying explanation relies on the behavioral implications of personality. While high conscientiousness has been associated with a healthier lifestyle this appears not to be the case for high neuroticism (63). Personality might influence lifestyle. For physical activity the evidence for neuroticism has been varying, perhaps indicating that there is not an association (68). Neuroticism might increase risk factors for cardiovascular disease, for instance smoking and substance abuse has been linked to high neuroticism (69). Alcohol consumption was linked to neuroticism in cross-sectional analyses, but the evidence was not replicated in a longitudinal analysis (67). Neuroticism has also been linked to other risk factors like high BMI (70) and hypertension (71).

Neuroticism describes a tendency towards responding towards internal and external stressors with heightened sensitivity towards negative affect. It is thought that this could influence the hypothalamus pituitary adrenal axis in the way individuals process stress. Frequent feelings of negative emotion could affect cortisol levels and lead to coronary artery atherosclerosis (72-74). Neuroticism is associated with the function of the autonomic nervous system as neuroticism influences for instance HRV, heart rate variability (75). It is possible that there also could be underlying immunological mechanisms involved (76). However, this topic requires further exploration.

4.5 Affective disorders, neuroticism and amygdala activation

Earlier research on the link between mental health and adverse cardiovascular outcomes suggests that some of the associated clinical consequences may be mediated on amygdalar level (2, 29). The nucleus amygdaloideus, located in the temporal lobe, is a limbic structure which shares a wide range of efferent and afferent connections to other parts of the nervous system. Some of its most important functions are related to the processing of emotions and learning. The amygdala receives information through various fibers, including sensory impulses from the senses through the thalamus. The amygdala also shares connections to the prefrontal cortex, which is involved in the conscious processing of the emotions. In simplified terms, the amygdala plays on important part in relation to assigning an emotional meaning to the information that we receive from the environment (2, 77).

Additionally, the amygdala can initiate somatic reactions in response to emotional stimuli. The amygdala sends fibers to both the brain stem and the ventromedial hypothalamus. Such amygdala launched reactions are associated to experiences that are often characterized as the "fight, flight or freeze responses". Numerous neurotransmitters are associated with amygdalar activation, including the release of CRH, corticotropin releasing hormone in the hypothalamus (77). Corticotropin releasing hormone will contribute to increased levels of corticosteroid hormones. CRH mediates its effects on the adrenal gland cortex through the release of ACTH, adrenocorticotropic hormone from the anterior hypophysis. Stress and anxiety increase the level of CRH (78). Similarly, deviations in CRH concentrations have been demonstrated in depressed individuals (77).

Increased amygdala activation can be studied with brain imaging, the fMRI or the FDG-PET/CT methods. In 2017, a longitudinal imaging study on the association between stress and

heart health was published in the Lancet, where 293 patients were followed for 3-7 years. A brain scan was conducted on all patients to assess their stress levels. Despite a rather small study population, there was a statistically significant association between the results from the imaging and the risk of developing CVD, HR 1.59 (CI 1.27–1.98), including MI and stroke, throughout follow-up. They noted a link between stress and increased inflammatory parameters which may predispose to the development of atherosclerosis (2, 29). Also earlier, affective symptoms have been associated with biochemically quantifiable changes in inflammatory markers (CRP, IL-6, TNF-alpha) (79).

I find it interesting that the 2017 study shifts the focus from differentiating between the potential underlying sources of stress, to treating amygdala activity as the common denominator. As others have pointed out earlier, the source of stress could be ascribed to a range of different affective diseases or for instance reactions to hardships throughout life (2). It can be challenging to differentiate between the effects of individual components which construct good psychological wellbeing as many factors are related to each other. For instance, high neuroticism, or an increased proclivity towards negative affect, is both linked to depression as well as challenges with stress regulation (80).

In the light of these findings, it is possible that the association between neuroticism and cardiovascular disease, in comparison to for instance affective disease symptom severity and cardiovascular risk profile, reflect two sides of the same coin. The possibility for that amygdala activity or another similar parameter as supposed to neuroticism could be a more optimal representation of the formulation cannot be excluded. On the other hand, personality traits also mediate other functions that are not necessarily stress or amygdala based. Yet, high neuroticism is often displayed in a negative light in the context of psychopathology, and it seems plausible that increased negative affect could also potentially be linked to imageable variations in brain activity. As amygdala activity is also influenced by acute stress it may be demanding to secure that the imaging method is detecting the effects of neuroticism (81). To my knowledge, the studies on the relationship between neuroticism and amygdala activation have showed inconsistent results (81-85).

As depression and neuroticism are both risk factors for heart disease and are also associated to each other (80), some of the papers in this review have adapted different kinds of approaches towards resolving the issue. Some authors challenged the idea of utilizing a singular aspect of psychological wellbeing as the exposure. For instance, Li et al. suggest that a better solution

could be to embrace a collective score based on the sum of different psychological health components. In their study they constructed a score based on four aspects of psychological health and analyzed the association between the score and CVD. Additionally, they performed sub-analyses of the effects of the individual factors while adjusting for the remaining influencing components (52). Meanwhile, for example Almas et al. divided the participants into four categories based on depression (yes/no) and neuroticism status (yes/no) (56).

4.6 Stability of personality traits and linkage to mental health

The results inevitably raise the question: in case personality is a *stable structure of characteristics* (8), should neuroticism be regarded as a non-modifiable risk factor for heart disease, such as age, gender, family history and ethnicity? Despite this well-known definition of personality, there is also some evidence for the plasticity of personality traits (7). It is suggested that significant events throughout life could potentially influence personality (6). Some authors in this review also chose to explore some of the potential psychosocial origins of high neuroticism. Some earlier research suggests that genes may account for only around 30-60% of the personality development (60). In addition to biological components, Morton et al. imply that adverse early life experiences could increase the level of neuroticism, which in turn may increase the risk of MI (57).

This brings us back to the complexity of the intricate connections between the components which constitute psychological wellbeing. As Morton et al. highlight the association between early adverse experiences and high neuroticism (57), elsewhere childhood trauma has also as an independent factor been linked to multiple adverse health outcomes including CVD (3). These findings could also be linked to amygdala activation. For instance, a small study on war-veterans with PTSD, post-traumatic stress disorder, showed increased activation of the amygdala in comparison to healthy controls. Additionally, the control group displayed increased connectivity from the amygdala to parts of the brain which are involved in higher order decision making. On the contrary, the individuals with PTSD showed increased activity between the amygdala and the ACC, anterior cingulate cortex (86). Abnormalities in the function of this limbic structure has been linked to mood disorders (87).

Although neuroticism itself just describes a personality trait rather than psychopathology, it is often prominent in affective disorders (23). The good news is that the associations from the amygdala to the medial prefrontal cortex can be strengthened through repeated exposure to the

fear-provoking stimulus. The crucial part is that the exposure should occur in the absence of the adverse feared consequences. This leads to the mitigation of the fear response and is described as “fear extinction” (77). A plentiful of therapeutic interventions have been designed to help strengthen the prefrontal input to the amygdala; a process which ultimately leads to a reduction of the reaction to fear. Such methods include different types of cognitive behavioral therapies (88). In relation to personality, it seems plausible that in case an individual with high neuroticism would experience the degree of neuroticism as afflicting, similar interventions could perhaps be adapted.

4.7 Strengths and weaknesses

This literature review included 10 different papers which analyzed the risk of getting cardiovascular diseases in the light of neuroticism. The results among the papers studying the relationship between high neuroticism and risk of heart disease pointed consistently towards a small positive association. The current review only included studies with over 1000 participants, with study population sizes ranging between 1028 and 461,168 participants to ensure sufficient statistical power. The literature search was targeted towards relevant papers. Despite a relatively limited selection of terms used for cardiovascular diseases, I am relatively confident that the literature search provided a fairly accurate representation of which longitudinal research that has been published during the past 10 years on the association between neuroticism and non-fatal coronary heart disease.

As this paper excludes studies which predominantly study the risk of mortality from cardiovascular diseases, it is not possible to generalize the results of this study to cardiovascular mortality. This needs to be explored further elsewhere. Likewise, the results for stroke risk remained inconclusive. As most of the studies on stroke risk pointed towards another direction, the association between high neuroticism and increased stroke risk remains uncertain. Although many cardiovascular diseases share similar risk factors, it is possible that personality influences the risk of developing different cardiovascular diseases in a non-identical way. Additionally, it is not completely possible to rule out the influence of additional potential confounders. However, some of the results demonstrated that the results remained positive despite accounting for the effects of anxiety and depression alongside a multitude of traditional risk factors (52).

Another limitation already discussed, is that it is not certain whether neuroticism is the optimal point of reference when studying the impact of psychological wellbeing on cardiovascular health. As some of the authors suggested, it could be that a summed mental health score could be a better predictor of cardiovascular health (52, 53). However, this raises again the question of which variables should exactly be included in the total risk evaluation. It is also possible that the different aspects of the psychological wellbeing assessment mediate their effects through stress and amygdala activation. For instance, the studies in this review generally indicated that depression is a stronger risk factor for CVD than neuroticism. It could be that depression generally causes greater stress for the individual than just presenting at the top of a personality spectrum. However, the study of personality is of interest as personality very likely also influences different non-stress-mediated characteristics such as lifestyle related factors.

Lastly, despite following many PRISMA-guideline criteria for systematic reviews, this review may not be classified as a fully systematic review (47). Although this review has adapted a more narrative point of view, the study methodology has been explained transparently. This review is also limited by the observational nature of the studies included in this paper. Despite a longitudinal design, the observational nature ended up reducing the level of evidence. Nevertheless, the literature included in the results of this study has been selected in a structured manner. Additionally, the presentation of the study methodology and the assessment of the quality of the evidence has been described carefully to ensure transparency.

6 Conclusions

This study provides an overview of the past 10 years of literature covering the association between neuroticism and cardiovascular disease. The results indicate that there is a small albeit significant link between neuroticism and the risk of developing cardiovascular disease. This risk applies to coronary heart disease including myocardial infarction, but the results for stroke risk were inconclusive. In the three largest study samples included, the HRs for MI and/or CHD varied from HR 1.03 (CI 1.02-1.04) to HR 1.14 (CI 1.07–1.21). According to the results neuroticism is a small, albeit significant risk factor for heart disease. Nevertheless, the risk was more moderate in comparison to traditional risk factors such as diabetes and smoking. This suggests that traditional modifiable risk factors should still be the primary target for preventative cardiovascular medicine. The evidence for personality mediated stroke risk was insufficient.

7 Conflicts of Interest

No conflicts of interest

8 Figures and Tables

Title	Author, (year, place)	Sample size and study population	Follow-up time	Measures	Results	Conclusion
Psychosocial Distress and Stroke Risk in Older Adults (51).	Henderson et al. (2013, USA).	2649 in the CHAP study.	~6 years.	The influence of 4 mental health factors, including neuroticism, on incident stroke risk.	High neuroticism was not associated with an increased risk of: **Stroke**: HR 1.30 (P<0.10).	The combined effect of the 4 mental health factors was associated with an increased risk for hemorrhagic stroke. Neuroticism was not significantly linked to this risk.
Effect of neuroticism on risk of cardiovascular disease in depressed persons - a Swedish population-based cohort study (56).	Almas et al. (2017, Sweden).	10,443 in the PART study.	~14 years.	The influence of neuroticism and depression on incident MI and stroke risk.	High neuroticism was associated with an increased risk of: **CVD**: HR 1.4 (CI 1.1-1.8). **Heart disease**: HR 1.7 (CI 1.2-2.3). **Stroke**: HR 1.3 (CI 1.0-2.0).	Depression and neuroticism are both risk factors for CVD. The risk increases additionally when they occur simultaneously.
Childhood Misfortune, Personality, and Heart Attack: Does Personality Mediate Risk of Myocardial Infarction? (57)	Morton et al. (2018, USA).	3,012 in the MIDUS study.	~9-12 years.	The influence of neuroticism and adverse childhood experiences on incident MI risk.	High neuroticism was associated with an increased risk of: **MI**: HR 1.441 (CI 1.017-2.040).	Adverse childhood experiences were associated with both high neuroticism and MI risk. Neuroticism was also linked to increased risk of MI.

Table 2: *An overview of the studies included from the literature search.*

Title	Author, (year, place)	Sample size and study population	Follow-up time	Measures	Results	Conclusion
Association of comprehensive mental health with incident cardiovascular disease: A prospective cohort study (52).	Li et al. (2022, China).	339,616 in the UK biobank.	~11 years.	The influence of 4 mental health factors, including neuroticism, on incident CHD and stroke risk.	High neuroticism was associated with an increased risk of: **CVD**: HR 1.07 (CI 1.03-1.11) **CHD**: HR 1.09 (CI 1.05-1.13) But not: **Stroke**: HR 0.94 (CI 0.87-1.02)	Neuroticism was positively associated with CVD and CHD risk, but not stroke risk. Depression and anxiety were more important cardiovascular risk factors than neuroticism.
Joint exposure to positive affect, life satisfaction, broad depression, and neuroticism and risk of cardiovascular diseases: A prospective cohort study (53).	Sun et al. (2022, China).	126,255 in the UK biobank.	~12 years.	The influence of 4 mental health factors, including neuroticism, on CHD, stroke and heart failure risk.	High neuroticism was associated with an increased risk of: **CVD:** 1.08 (1.02–1.14) **CHD**: 1.14 (CI 1.07–1.21) But not: **Stroke**: 0.92 (CI 0.82–1.03) **Heart failure**: 1.04 (CI 0.93–1.17)	High neuroticism increased the risk of and CHD, but not stroke or heart failure.
The influence of personality on the risk of myocardial infarction in the UK Biobank (58).	Dahlen et al. (2022, Sweden).	460,865 people in the UK biobank.	~7 years.	The influence of personality traits on incident MI risk.	High neuroticism and high nervousness were respectively associated with an increased risk of: **MI**: HR 1.03 (CI 1.02-1.04). **MI:** HR: 1.07 (CI 1.04-1.09).	Neuroticism and nervousness were associated with an increased risk of MI. Characteristics representing conscientiousness, agreeableness and extraversion decreased the risk.

Table 2 (continues): *An overview of the studies included from the literature search.*

Title	Author, (year, place)	Sample size and study population	Follow-up time	Measures	Results	Conclusion
Association of Diligence and Sociability with Stroke: A UK Biobank Study on Personality Proxies (54).	de Ruijter et al. (2022, Sweden).	461,168 in the UK Biobank.	~ 7 years.	The influence of personality traits on incident stroke risk.	High neuroticism was not associated with an increased risk of: **Stroke**: 0.99 (CI 0.94 - 1.03)	Neuroticism was not associated with an increased risk of stroke. Characteristics representing conscientiousness and extraversion decreased the risk of stroke.
Cardiovascular risk indicators among depressed persons: A special case? (50).	van Zutphen et al. (2023, the Netherlands).	1028 people in the NESDA and NESDO studies.	~5 years.	The influence of neuroticism and depression on incident CVD risk.	High neuroticism was not associated with an increased risk of: **CVD:** 1.31 (CI 0.90-1.90).	High neuroticism did not increase the risk of CVD, but depression and anxiety did.
***Personality and Risk of Incident Stroke in 6 Prospective Studies* (55).**	Stephan et al. (2023, multiple countries).	58 105 participants in the MIDUS, HRS, US, WLS, NHATS and LISS studies.	~7-20 years.	The influence of personality traits on incident stroke risk.	High neuroticism was associated with an increased risk of: **Stroke:** 1.13 (CI 1.07–1.21).	Neuroticism was associated with an increased stroke risk, whereas conscientiousness decreased the risk.
Personality and Health: Disentangling Their Between-Person and Within-Person Relationship in Three Longitudinal Studies (6).	Luo et al. (2022, multiple countries).	2,209 participants in the SATSA study.	SATSA: ~14 years.	The influence of personality traits on CVD risk (a wide range of conditions).	High neuroticism was associated with an increased risk of: **CVD:** r .22 (CI .13 -.30).	Neuroticism was positively associated with increased risk of CVD.

Table 2 (continues): *An overview of the studies included from the literature search.*

Studies:	Downgrading factors in addition to study design	Upgrading factors	Neuroticism mediated risks on cardiovascular outcomes	Quality
Henderson et al., 2013 (51).	**Imprecision:** Confidence intervals for the individual mental health factors, including neuroticism, are not presented. The analyses for incident stroke are only described but not presented in table form.	**Dose response gradient** between the mental health score (but not neuroticism) and hemorrhagic stroke.	**Stroke (hemorrhagic):** HR 1.30 (P<0.10).	C
Almas et al., 2017 (56).	**Indirectness**: It is possible that the low participation rate (53%) was attributed to depression status. **Reporting bias**: To my knowledge, the values presented in the abstract cannot be found in the graphs. Additionally, the authors presented a not fully adjusted value in the introduction when referring to their previous research.	-	**CVD**: HR 1.4 (CI 1.1-1.8) **Heart disease**: HR 1.7 (CI 1.2-2.3) **Stroke**: HR 1.3 (CI 1.0-2.0)	D
Morton et al., 2018 (57).	**Imprecision:** Rather wide confidence interval. **Risk of bias**: Not all major potential confounders were considered. Additionally, childhood data was retrospective. **Indirectness:** The outcome was based on merely self-reported data.	-	**MI:** HR 1.44 (CI 1.02-2.04).	D
Li et al., 2022 (52).	-	**Dose response gradient** between (adverse) mental health and risk of CVD.	**CVD**: HR 1.07 (CI 1.03-1.11) **CHD**: HR 1.09 (CI 1.05-1.13) **Stroke**: HR 0.94 (CI 0.87-1.02)	B

Table 3: *Overview of the grading of the studies.*

Studies:	Downgrading factors (in addition to study design)	Upgrading factors	Neuroticism association with CVD	Quality
Sun et al, 2022 (53).	-	-	**CVD:** HR 1.08 (CI 1.02–1.14) **CHD**: HR 1.14 (CI 1.07–1.21) **Stroke:** HR 0.92 (CI 0.82–1.03) **HF:** HR 1.04 (CI 0.93–1.17)	C
Dahlen et al, 2022 (58).	**Indirectness:** Invalidated exposures were used (nevertheless, neuroticism was measured with validated methods)	-	**MI:** HR 1.03 (CI 1.02-1.04)	C
De Ruijter et al, 2022 (54).	**Indirectness:** Invalidated exposures were used (nevertheless, neuroticism was measured with validated methods)	-	**Stroke:** HR 0.99 (CI 0.94 - 1.03)	C
van Zutphen et al., 2023 (50).	**Risk of bias**: The outcome was defined as a pooled group. Small population. **Inconsistency:** inconsistent results. **Indirectness:** the outcome was based on merely self-reported data.	-	**CVD:** HR 1.31 (CI 0.90-1.90)	D
Stephan et al., 2023 (55).	**Inconsistency**: Inconsistent results. **Indirectness:** The outcome was based on merely self-reported data. **Risk of bias:** All potential confounders not considered.	-	**Stroke:** HR 1.13 (CI 1.07–1.21)	D
Luo et al., 2022 (6).	**Risk of bias**: Insufficient description of how potential confounders were considered. Pooled outcome only. **Indirectness**: The outcome was based on merely self-reported data.	-	**CVD**: r 0.22 (CI 0.13 -0.30)	D

Table 3 (continues): *Overview of the grading of the studies.*

	Smoking	Hypertension	Cholesterol or use of lipid lowering drugs	Diet	Physical activity	Diabetes	Weight	Alcohol intake	Family history	Age	Gender	Ethnicity/ race	Socio-economic status/ education
Henderson et al 2013	x	x	x		x	x	x			x	x	x	x
Almas et al, 2017	x	x			x	x	x	x		x	x		x
Morton et al, 2018	x	x				x	x		x	x	x	x	x
Li et al, 2022	x	x	x	x	x	x	x	x	x	x	x	x	x
Sun et al, 2022	x	x	x	x	x	x	x	x		x	x	x	x
Dahlen et al, 2022	x	x			x	x	x	x		x	x	x	x
De Ruijter et al, 2022	x	x			x	x	x	x		x	x	x	x
van Zutphen et al, 2023	x	x	x		x	x	x	x		x	x		x
Stephan et al, 2023	x	x			x	x	x			x	x	x*	x
Luo et al, 2022										x	x		

Table 4: *Traditional risk factors included as covariates in the separate studies. Not all covariates (for instance use of antipsychotic medication, mental health symptoms or sleep quality) are included in this graph.*

**Adjusted in 4/6 cohort studies.*

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