Master Degree Project

UNIVERSITY OF SKÖVDE

Association between neuroticism and risk of incident cardiovascular disease in the UK Biobank cohort

Master Degree Project in Systems Biology
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Master Degree Project in Systems Biology

Abstract

Myocardial infarction (MI) and stroke are the major causes of cardiovascular related morbidities and mortalities around the world. The prevalence of cardiovascular diseases has been increased in last decades and it is vital need of time to investigate this global problem with focus on risk population stratification. The aim of the present study is to investigate the association between individualized personality trait that is neuroticism and risk of MI and stroke has been investigated in a large population-based cohort of UK biobank.375,713 individuals (mean age: 56.24 ± 8.06) were investigated in this longitudinal study and were followed up for seven years to assess the association between neuroticism and risk of MI and stroke incidence. The neuroticism score was assessed by a 12-item questionnaire at baseline, while information related to MI and stroke events was either collected from hospital records and death registries or was self-reported by the participants. Cox proportional hazard regression adjusted for age, gender, BMI, socioeconomic status, lifestyle factors and medical histories for hypertension, diabetes and depression was used. All statistical analyses were performed using R software. In fully adjusted model, a one standard deviation increase in neuroticism score was associated with 1.05-fold increased risk for MI. (HR=1.047(1.009-1.087), p=0.015). However, no significant association was observed between neuroticism score and incident stroke as well as between neuroticism score and overall cardiovascular disease (MI and stroke combined). Results from the present study indicate that neuroticism is a risk factor for MI but not for stroke. These findings suggest that personality traits such as neuroticism may prove to be helpful in efficient risk stratification and pre-clinical diagnosis of individuals at risk for MI.

Popular scientific summary

Negative personality may increase the risk of having a heart attack

Personality and behavior is usually the first thing you notice upon meeting someone. Some people are more moody than average while some people are very friendly and open to you indicating that every person has his own perspective and way to perceive the things happening around him. Every individual is different from other in terms of how he or she reacts to the events happened to him. There are many people who get stressed out or angry very easily when there is some difficult situation while others are very patient and relaxed, and this may affect their quality of life and health outcomes too. Neuroticism is one of the five personality traits characterizing people who get stressed out very frequently, get hopeless out of minor frustrations and interpret ordinary situations as threatening situations. Having a neurotic personality may affect your health and may increase your chances to get many diseases. Researchers all over the world have been trying hard to understand this relationship of personality and health outcomes. Many studies have been done so far, of which some have been very confusing while others give some clues. In the present study, we tried to understand the link between neuroticism and heart diseases including heart attack and stroke. Additionally, we tried to investigate whether the environment in which the people are working, and their occupation has an effect on this link or not.

The present study was conducted by using data from the United Kingdom. Around half a million residents of United Kingdom filled out a questionnaire regarding their lifestyle, medical history and details of diagnosis. It also contained some questions specially designed by psychologists for personality assessment including neuroticism score. After initial assessment, the participants were followed up for seven years and we determined their risk of having heart attack or stroke during this time.

The result of our study showed that people with high neuroticism may have higher risks of getting heart disease than the people with low neuroticism. One possible mechanism can be that the neurotic people usually have higher levels of anxiety and depression that may lead to high blood pressure and ultimately increase their chances of having a heart disease. However, we did not find any effect of occupation on the link between neuroticism and heart diseases.

We strongly believe that raising a problem is important but striving for the solution to that problem is more important. Thus, based on our study findings, we propose that health care authorities should take some important measures to prevent the neurotic people from the heart diseases. These measures may include counseling about how to decrease anxiety and stress and guidance towards more positive and healthier lifestyle. All this can be achieved by implementing personality assessment as an important part of clinical evaluation specifically for people at higher risk of having heart diseases.

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Abbreviations

BMI Body mass index

CVD Cardiovascular disease

MET Metabolic equivalent of tasks

MI Myocardial infarction

TDI Townsend deprivation index

UKB United Kingdom Biobank

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide (Von *et al.,* 2012). Myocardial infarction (MI) is a key component of CVD burden. The prevalence of the MI approaches 3 million people worldwide with around 1 million deaths just in United States annually (Mechanic *et al*., 2020). The assessment of incidence, risk factors and case fatalities of MI are important determinants of the decline in MI related mortalities. (Barberi *et al.,* 2018). As far as the cardiovascular risk factors are concerned, the vital role of hypertension, smoking and high blood cholesterol levels is established on the incidence of non-fatal and fatal MI in a middle-aged population of German men (Keil *et al*., 1998). Likewise stroke also has great impact on CVD prevalence and is not that much associated with mortality but the morbidity. The nonmodifiable risk factors for stroke include race, age, sex and family history whereas the modifiable risk factors for first ischemic stroke include hypertension, cardiac disease (particularly atrial fibrillation), diabetes, hyper lipidemia, cigarette smoking, alcohol abuse, physical inactivity, asymptomatic carotid stenosis, and transient ischemic attack (Sacco *et al.,* 1998). Apart from medical history, certain socioeconomic and demographic risk factors have also been associated with MI. According to acute MI practice guidelines in Sweden, the psychosocial status of the patients should be evaluated for diagnosis and prognosis of MI (Thombs *et al.,* 2006). The relationship of work, family and life events with CVD risk factors cannot be ignored as Welin *et al*. investigated this association and found an increased mortality rate among the MI patients with limited social contacts and depressive symptoms (Welin *et al.,* 1995). In further investigation, MI has been shown to be not only positively associated with life events, but also the mental strain at work, depression and lack of social support (Welin *et al.,* 1996).

According to extensive research in cardiac epidemiology, there are certain psychological factors which play an important role in increasing the risk of cardiovascular diseases and these factors are linked to personality characteristics and social environments. To explain this link, several mechanisms have been proposed focusing on genetic disposition, bad life style , low compliance to health recommendations and other pathophysiologic covariates. (Von *et al.,* 2012). There are psychosocial factors such as depression, chronic stress, anxiety and personality factors which can enhance the risk of heart diseases. Pathophysiological aspects shows that these psychosocial risk factors may leads to the development and clinical consequences of arteriosclerosis. (Saner et al., 2005)

Prominent role of gender difference in CVD risk has been investigated in another study that highlighted that lack of social support, female sex and depression independently increased the risk of MI in women as compared to men (Möller *et al.,* 2007).

Neuroticism

Neuroticism is defined as a stable tendency to experience negative emotionality, including anxiety, low mood, and depression. According to the health behavior model of personality, levels of certain personality traits, particularly conscientiousness and neuroticism, are associated with either engagement in health promoting or health debilitating behaviors (Bogg *et al.,* 2004, Smith *et al.,* 2006). Personality traits are individualized characteristics of a person and differs from person to person (Costa *et al.,* 2008). It has been studied that people with high neuroticism are more self-critical, feel self-deficient and more conscious to the other's opinions (Watson *et al.,* 1994). Neuroticism is investigated to be associated with multiple mental and physical health problems (Malouff *et al.,* 2006).

Individuals in the population differ widely based on this personality trait. These may range from intense emotional reaction in response to minor or rather simple situations to very slight reaction in response to some significantly difficult event. Although the not widely supported but there is growing debate of profound public health significance linked with neuroticism as it is a predictor of various mental and physical disorders , the related co morbidities and mostly observed the frequency of health care services use (Lahey et al., 2009). That's why it is need of time to

understand the nature and origin of neuroticism as well as the mechanisms behind its possible yet unclear link with mental and physical disorders.

Neuroticism and CVD

Association of personality traits such as neuroticism with health outcomes have been an interesting area to investigate for researchers over the decade. Several studies have focused on investigating the association between neuroticism and health outcomes e.g., high neuroticism and low extraversion has been linked with tumor necrosis factor (TNF)-alpha in heart disease patients (Dennollet *et al.,* 2009). These health-related problems associated with neuroticism include depression and hypertension. (Hagger *et al.,* 2010). For decades the literature stating the relationship between neuroticism and CVD has been very inconsistent and this has made this area more dynamic (Johnson *et al.,* 2012). In a meta-analysis review of prospective cohort studies, it has been observed that people with high degree of neuroticism are more vulnerable to high blood pressure and atherosclerosis. This study also predicted that anger and hostility are positively associated with coronary heart disease outcomes both in healthy and sick populations (Shipley *et al.,* 2009). On the contrary, a population-based prospective cohort study in Japan does not support the hypothesis that personality is a risk factor for mortality from ischemic heart disease and stroke (Nakaya *et al.,* 2005). Moreover, Batty et al., also reported the negative association between neuroticism and CVD (Batty *et al.,* 2015).

The mechanism underlying association between high neuroticism and adverse health outcomes is still a puzzle and various hypotheses mainly investigating psychosocial factors have been proposed. Persons with a high degree of neuroticism may possibly more frequently experience higher levels of psychosocial stress which in turn can lead to elevated blood pressure and unhealthy behaviors such as poor diet, physical inactivity, smoking, sleep disturbances, or lower treatment adherence (Chida *et al.,* 2009). The British Health and Lifestyle Survey concluded that neuroticism can be associated with a higher mortality risk in cardiovascular diseases (Shipley *et al.,* 2009) which were later evaluated in a pooled analysis from three cohort studies (Jokela *et al*., 2014). Another study found high neuroticism as a risk factor for the cardiac mortality in women with low socioeconomic status while protective for the women with higher socioeconomic status (Johnson *et al.,* 2012). In a large population-based cohort of 10,341 adults, an evidence of a synergistic interaction between neuroticism and depression on future risk for CVD was found which implies that high level of neuroticism increases the risk of CVD in depressed patients (Almas *et al.,* 2017). In another U.S cohort study of 1,255 participants, higher neuroticism was found to be associated with reduced heart rate variability (HRV) equally under rest and stress conditions which is indicative of CVD. The baseline structural equation model in this study revealed significant paths from neuroticism to HRV, CVD and depression and concluded that neuroticism has independent associations with both autonomic reactivity and CVD, over and above its associations with depression and other related variables (Čukić *et al.,* 2015). So by considering neuroticism as top priority of the research, a better understanding of commonalities among health related outcomes of it can be achieved and it might lead to development of improved strategies to prevent its predicted link with mental and physical disorders (Lahey et al., 2009).

Surprisingly there are studies that support neuroticism as protective factor for disease outcomes. This concept of healthy neuroticism although was very first introduced by Fredman in 2000 (Fredman *et al.,* 2000), according to which people with high neuroticism might be more conscious in taking care and following up their health issues. This vigilance to get relatively higher medical care facilities could increase the survival of these individuals due to early identification of fatal diseases (Cuijpers *et al*., 2010). Higher neuroticism was associated with an 8% reduction in all-cause mortality after adjustment for other covariates, and, in particular, self-rated health (Gale *et al.,* 2017). Whereas some studies have found no relation between them (Jokela *et al.,* 2013, Costa *et al.,* 2000). A suggested mechanism linking the high neuroticism with the risk of CVD has been demonstrated in Figure1.

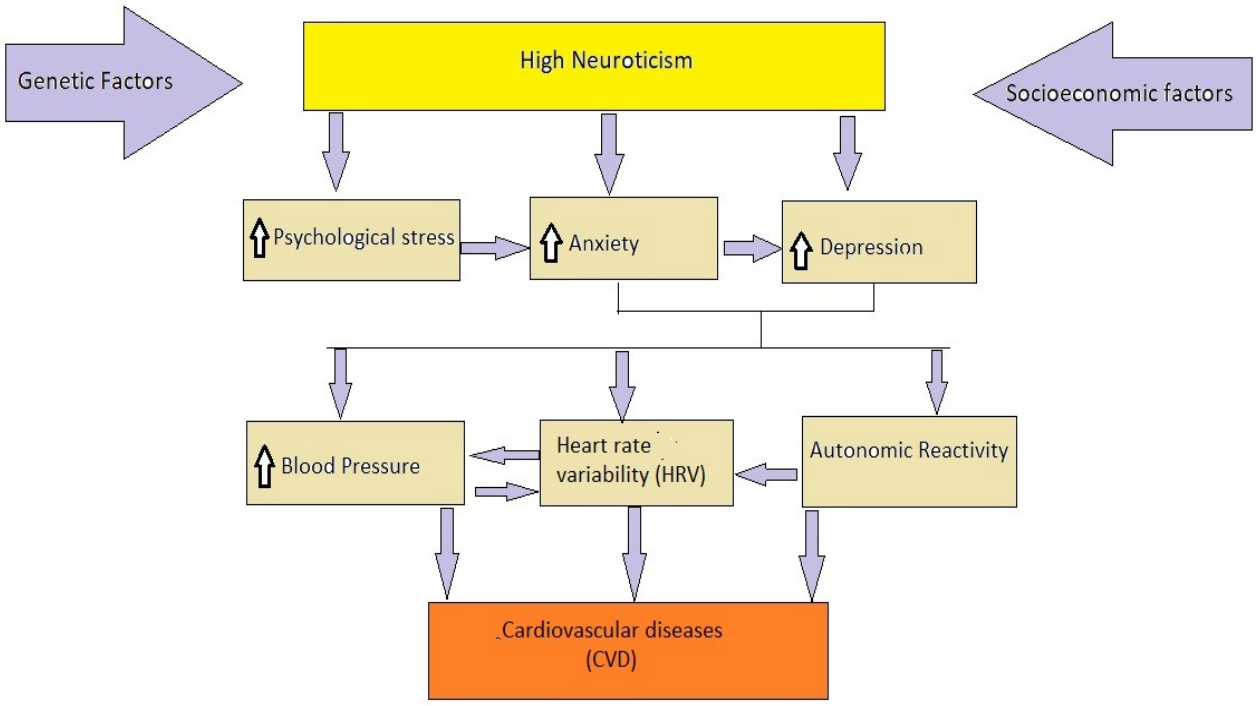


Figure 1. Proposed mechanism of how high neuroticism is associated with development of cardiovascular diseases. The figure has been adapted from Čukić *et al.,* 2015

Neuroticism and CVD among occupational groups

Occupational risks and hazards are widespread and their impact on mental and physical health, well-being and occupational outcomes may be modified by individual differences in personality and genetic liability (Chiorri *et al.,* 2015). This has been the subject of scientific debate that work stress is a risk factor of many chronic diseases. This interesting review by Kivimaki et al give an evidence from over 600,000 men and women from 27 cohort studies recommends that work related stressors such as long working hours and job strain are linked to elevated risk of incident coronary heart diseases and stroke. These cohorts were from Europe, the USA and Japan and the exposed individuals were found to be having is 10–40 % of excess risk as compared with those fre

Simmilarly a meta-analysis study that was focused on workers with acute coronary heart disease event, showed that work stress increase the risk of developing recurrent cardiovascular events by 65% (Li et al., 2015).e of such stressors. (Kivimäki *et al.,* 2015).

Apart from the association between neuroticism and CVD in general population, understanding the differential impact of neuroticism on CVD risk across different occupational groups is also especially important for the identification of risk groups. Unfortunately, there is not enough literature stating the relationship between neuroticism and occupational health. In a 15-year prospective study of young Finns Hintsanen *et al.,* suggests that temperament may be a predisposing factor to the experiences of work stressors .in this study self-reported job strain and effort–reward imbalance was measures of job characteristics, they were observed to be affected by individual temperament. The results of this prospective study showed that higher negative emotionality and lower sociability systematically predicted higher perceived job strain. Another study on a group of special police officers from a special police force showed that there is a direct link between neuroticism and low agreeableness and work stress. This study supported the hypothesis that the combination of emotional stability (low neuroticism) and friendliness

improves the level of self-perceived stress and increases resistance to stressful changes of working tasks. (Törnroos *et al.*,2012),

A study investigated the association of neuroticism with health outcomes among emergency personnel and observed that high neuroticism was positively associated with poorer subjective health outcomes in all emergency persons (Mutambudzi *et al .,* 2019). In literature, the study of personality factors showed little utility for predicting a successful career in the armed forces (Hartmann *et al.*, 2003). In a study about highway patrol officers neuroticism independently predicted and resulted in higher risks of mental exhaustion or nervous breakdown and neuroticism scores were related with increased reporting of physical symptoms and emotional exhaustion and negatively associated with total job satisfaction (Hills *et al.,* 1991) When examining depressive symptoms in police recruits after one year of the start of service, greater neuroticism scores at training were associated with greater levels of 'current' symptoms of depression and post-traumatic stress disorder (PTSD) and feelings of self-worth (Ortega *et al.,* 2007)

Research investigating the relationship between work stress and individuals health has prospered over the past 20 years. At the same time, research on individuals personality traits and physiological stress mechanisms has also advanced significantly. Working conditions such as work stress and shift work have been shown to affect employee health and performance in a review by Ganster et al which spans multiple disciplines and includes a critical discussion of management and applied psychology research, epidemiological studies, and recent developments in biology, neuroendocrinology, and physiology that provide insight into how workplace experiences affect well-being. (Ganster *et al.,* 2013). However, there is always a need for additional epidemiological studies with high statistical power to determine the specific occupations at higher risk for CVD particularly after taking into account the modifying impact of personality traits. Effect of working hours and specific working groups has been thoroughly studied by the the Hordaland health study which concluded that significantly higher anxiety and depression levels along with higher prevalence of anxiety and depressive disorders were observed in overtime workers irrespective of genders in comparison with those working normal hours. These findings also suggested a dose-response relationship between work hours and anxiety or depression. Working overtime was also associated with increased levels of anxiety and depression and working groups differed significantly regarding several factors including income and heavy manual labor (Kleppa *et al.,* 2008).

As social class has been defined by different indicators such as occupation and job position or the highest school qualification achieved and It's been known for a long time, that certain diseases are more frequent in lower socioeconomic classes than the higher . But knowledge is still very limited about the nature of this association, risk factors associated with it and how to improve health outcomes in lower socioeconomic groups. Behavioral factors such as smoking, obesity and physical inactivity are more commonly present in the lower socioeconomic groups. People with a lower educational level visit their GP more often, whereas people with a higher level of educational consult specialists more frequently. (Meier *et al.,* 2005)

Relationship between job satisfaction and neuroticism is very thoroughly validated by Judge et al. In this metanalysis, it was seen that neurotic individuals experience more negative life events because they select themselves into situations that foster negative affect and in context to the job, they would lead to diminished levels of job satisfaction. In this study, neuroticism emerged as the strongest and most consistent correlate of job satisfaction and after studying all personality traits, the validity of neuroticism came as no surprise. Emotional stability (low neuroticism) and extraversion were found to be the factors that cause emotionally stable and extraverted individuals to be happy in life would also lead them to be happy in their jobs as the conclusion of this meta-analysis findings were "Greater job satisfaction is related to lower neuroticism and its variants, as well as to higher extraversion and related traits". (Judge *et al.,* 2002)

Aim

The main aim of the present study was to investigate the association between neuroticism and incident CVD (MI and stroke) in a large population cohort of United Kingdom, the UK biobank (UKB). Secondary aim was to investigate this association across different occupational categories in UKB. We hypothesize that high neuroticism is associated with higher risk for MI and stroke and this association is affected by employment class and mediated by covariates. A longitudinal study design will be followed with the implication of cox proportional regression model to assess the risk of incident MI and stroke in sample population. As the scientific literature stating the relationship of neuroticism and health outcomes is very dynamic so our study may contribute in explanation of this association with a big sample size hence big statistical power. Moreover this may identify some potential risk groups and help health care authorities to make certain strategies to prevent the global burden of cardiovascular diseases.

Materials and methods

Data source

Data for the present study has been originated from UKB. UKB is a large prospective study which aimed to provide a resource for the investigation of the genetic, environmental and lifestyle determinants of a wide range of diseases of middle age and later life. Between 2006 and 2010, over 500,000 men and women aged 40 to 69 years were recruited and extensive data on participants' lifestyles, environment, medical history, and physical measures, along with biological samples, were collected. Participants were invited to attend one of the 22 assessment centers around the UK, where they completed extensive touch-screen questionnaires as well as undertook physical measurements. For the identification of appropriate cohort size, the statistical power calculation was performed so that for a certain disease or health condition investigation, a significant number of cases could be investigated. The age range for inclusion represented a pragmatic compromise between participants being old enough for there to be sufficient incident health outcomes during the early years of follow-up and young enough for the initial assessment to occur before incipient disease had a material impact on exposures. An executive management team of UK Biobank, with epidemiology, clinical, management, laboratory, legal, and communications expertise, oversees the development and day-to-day management of the resources (Sudlow *et al .,* 2015*).*

Study population: the UK Biobank

The participants (n=502,617) after signing the electronic informed consent form, were invited to attend assessment centers around the UK, where they completed extensive touch screen questionnaires as well as undertaking physical measurements. Since the present study consider the neuroticism score as the main exposure, all the participants who lack the information regarding neuroticism score in UKB were excluded from the study (n= 112,631). Furthermore, we excluded the participants having MI and stroke either before or at the baseline assessment (prevalent cases) so that we could identify a clear association between neuroticism and incidence of MI and stroke. Thus, 375,713 participants without reporting any MI or stroke event at baseline assessment were included in the study.4,459 MI and 2,322 stroke incident events were recorded during a median follow-up time of 7 years (Figure 2).

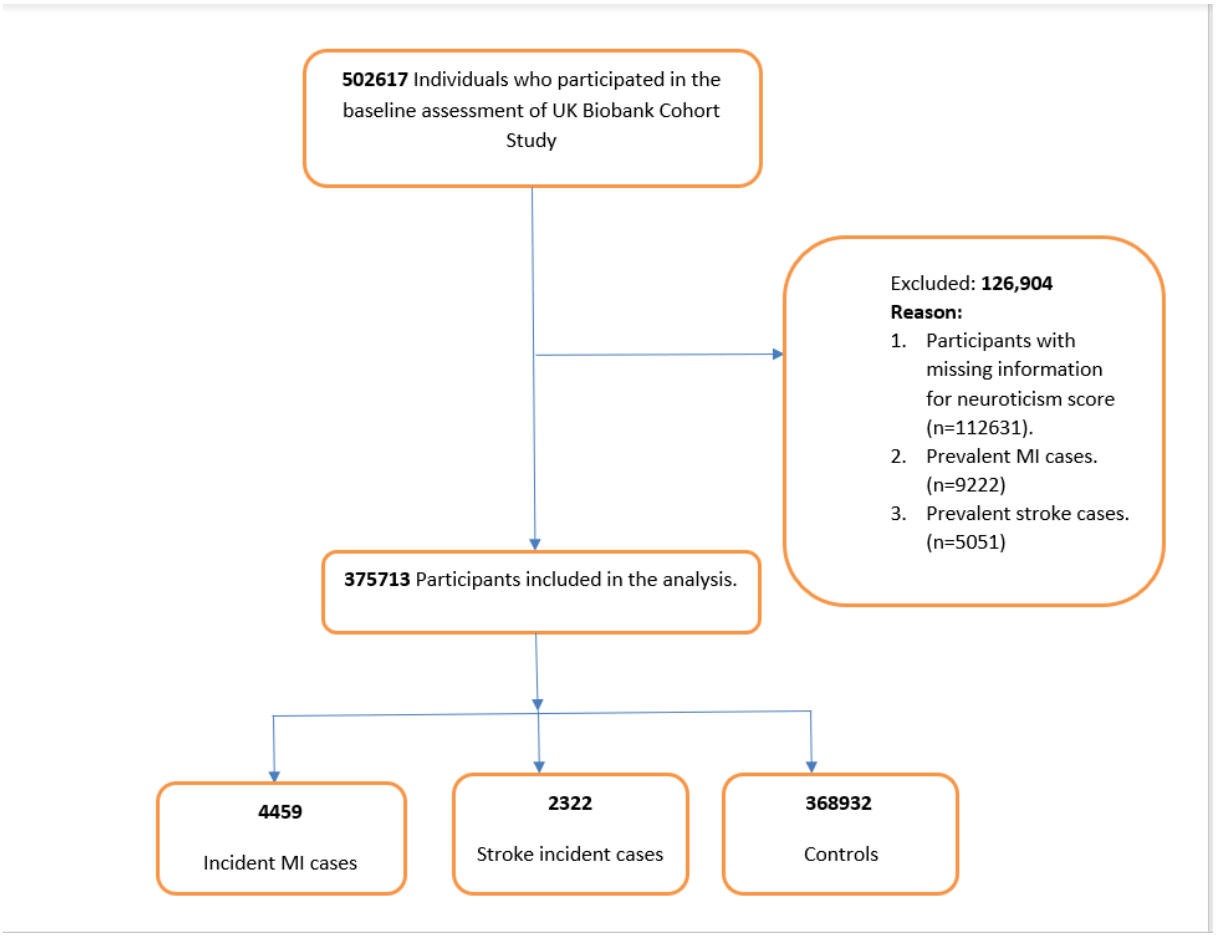


Figure 2. Consort diagram of study population with inclusion and exclusion criteria in longitudinal study among UKB participants. (UKB=United Kingdom Biobank, MI=Myocardial infarction)

Independent variable-neuroticism

The primary variable of interest in this study is "neuroticism" which was investigated by the parameter neuroticism score in the UKB (UKB Field ID = 20127). Neuroticism score is an externally derived summary score that covers twelve domains of neurotic behaviors and was assessed via touchscreen questionnaire. This 12-item personality questionnaire is known as Eysenck Personality Questionnaire-Revised Short Form (Eysenck *et al*., 1985). The score ranges from 0 to 12 with higher value representing higher level of neuroticism. In present study, the neuroticism score was converted into the z-score by using function "scale" and this standardized Z score was used in further analysis. Normally, to create z-scores or standardized scores from a variable, the mean of all data points are subtracted from each individual data point, then divide those points by the standard deviation of all points. Again, this can be accomplished in one call using "scale". Compared to percentiles, Z-scores have a number of advantages such as they are calculated based on the distribution of the reference population (mean and standard deviation), and thus reflect the reference distribution and secondly Z-scores can be analyzed as a continuous variable in studies. (Wang et al., 2012)

Study covariates

Gender

In the UKB, gender was acquired from the NHS central registry at recruitment, but in some cases updated by the participant in the touch-screen questionnaire. The original self-reported gender

variable used in the present analysis (UKB Field ID=31) was a dichotomous variable with 0 value defining female sex and 1 indicated male sex.

Age

Information regarding age was derived from "age at recruitment" variable from UKB Field ID: 21022. The original continuous variable was used in the analysis which was calculated by subtracting the date of attending the baseline assessment from the self-reported date of birth.

Body mass index (BMI)

In UKB, BMI variable (UKB Field ID: 21001) was constructed from height and weight measured during the initial assessment centre visit. In the present study BMI is used as the original continuous variable from UKB.

Socioeconomic status (SES)

Townsend deprivation index (TDI) was used as a proxy to measure the socioeconomic status from UKB. TDI score (UKB Field ID: 189) is a composite measure of deprivation based on unemployment, non-car ownership, non-home ownership, and household overcrowding. This was calculated before participants joined the UKB and was based on the preceding national census data, with each participant assigned a score corresponding to the postcode of their home dwelling. The negative TDI value represents high socioeconomic status while the positive TDI value represents the low SES (Tyrrell *et al.,* 2016).

Alcohol drinker status

Alcohol consumption information in UKB was collected by the touchscreen questionnaire at the baseline assessment (UKB Field ID: 20117) where the participants answered as "current"," previous"," never" and "prefer not to answer". For the current study, the original variable was recoded into a new dichotomous variable as there were less than two percent people who answered "previous" so it was better to recoded the variable into dichotomous variables where never has been recoded as "0" or "no" while current and previous were recoded into "1 "or "yes".

Smoking status

The current/past smoking status of the participant in UKB was summarized as UKB Field ID: 20116 where the response of the participants was recorded as "current", "previous", "never" and "prefer not to answer". In the current study, the original variable is recoded as categorical variable where "never" corresponded to 0, "previous" corresponded to 1 and "current" corresponded to 2.

Physical activity

Information regarding physical activity was extracted from the touchscreen-based questions related to the weekly frequency and duration in minutesof walking, moderate physical activity, and vigorous physical activity. The information was then used to calculate the metabolic equivalent per time (MET) score. First, extreme outliers were excludedout of the range of ±3.29 for of the duration of walking, duration of moderate physical activity and for the duration of vigorous physical activity). According to Aguinis et al, 2013, there can be three types of outliers. 1) error outliers, which are the result of errors in data coding; (2) interesting outliers, which contain unexpected knowledge because they were sampled from a different population; and (3) influential outliers, which are accurate data points that are not error or interesting outliers but that do have a substantial influence on the conclusions. Our outliers were of type 3, i-e "influential outliers" as they were reported by the participants belonging to the same population and were not a recoding error. (Aguinis *et al*, 2013) . The criterion of $z > 3.29$ or $z < -3.29$ implies that the values belong to the most extreme of the reference distribution and considered as extreme outliers (Verkoeijen *et al*, 2018). MET score (minutes/week) was then derived using the coefficients for each category obtained from the international physical activity questionnaire

short form, by using the formula mentioned by Rukh *et al* in her recent paper : MET score = [(Number of days/week of walking 10 + minutes × Duration of walking × 3.3) + (Number of days/week of moderate physical activity 10+ minutes × Duration of moderate physical activity × 4.0) + (Number of days/week of vigorous physical activity 10+ minutes × Duration of vigorous physical activity × 8)] (Rukh *et al*., 2020).

Hypertension

The information regarding high blood pressure or hypertension has been extracted from the UKB Field ID : 6150 which demonstrate the responses to touchscreen-based questions regarding vascular or heart problems diagnosed by the doctor. For present analysis the participants answered "high blood pressure" to the question "has a doctor ever told you that you have had any of the following conditions" were considered as hypertensive and recoded as "1" or "yes" in variable used. Else are recoded as "0" or "no".

Diabetes

During the initial assessment visit, the diabetes disease status has been recorded through the touchscreen-based questions in UKB Field ID: 2443. The participants who responded "yes" to the touchscreen question "has a doctor ever told you that you have diabetes?" were recoded as "1 or yes" and the ones who answer "no" were coded as "0". in our binary variable used for present study.

Depression

In present study the covariate variable "depression" was extracted from the UKB Field ID 20126 that demonstrated the bipolar and major depression status diagnosed by the doctor of the participants. The original UKB variable was recoded into binary variable for present study where "no depression" was demonstrated by 0 while all different depression types were recoded as "1".

Occupational categories

Employment status in UK Biobank was recorded at recruitment day. All the participants who were employed were detailed interviewed by trained operators. On the basis of all the additional information collected the interviewer manually classified them into different job codes using the standard occupational classification (SOC), V.2000. The UKB Data Field ID 132 was used to construct variable for the present study where we classified our study population into ten occupational categories based on 3-digit SOC classification.

Outcome variables - myocardial infarct and stroke events

The UKB adjudication committee had developed the algorithmically defined outcomes variable which were used in the present study to identify the MI and stroke events and the corresponding dates of event occurrence. The developed algorithm actually takes into account all the MI events that occurred in the study population by combining information from different sources, which was: self-reported information by the participants at baseline assessment, hospital records and death registries. Then, the algorithm recorded the earliest date of MI event found in all source documents for each participant into a date variable, while the type of source documents used to identify the earliest date of MI events was recorded into a categorical variable. The same algorithm and procedures were used to identify all stroke events that occurred in the study population.

Time-to-event variables

In the present study, the occurrence of the first MI or stroke event was considered as the study endpoints as already explained by the algorithmically defined outcome variables description above. The time variable for occurrence of first MI event was constructed by subtracting the date of first MI event from the date of participants' recruitment at baseline assessment center and resulted in days. The same strategy was used for constructing the time variable for stroke event.

Follow-up time is started at inclusion in the UK Biobank study and ended either on the first MI or stroke event or at 1st of March 2016 for all participants. So, the date value 1st of March 2016 was inserted into the original variable to replace the missing values and represents those participants without any reported MI or stroke event. Three time-to-event variables were constructed for the present analysis for MI, stroke and both MI and stroke. In the third variable called time-to-MI and stroke event, the corresponding R function was used to construct the variable so that whichever event occurred first, that event should be considered.

Prevalent MI and stroke cases

Prevalent MI and stroke cases were identified utilizing the time to event variables. Prevalent cases are defined as the participants who had MI or stroke events before they attended the baseline assessment. In the time to event variables, the negative values demonstrated the corresponding MI or stroke event that occurred before the baseline assessment while the 0 value indicated the self-reported event. So, to construct the prevalent cases variables, the time to event variables are recoded into binary variable where negative to 0 values were demonstrated by "1" or event while positive or missing values were coded as "0" or controls. For the present longitudinal study, we excluded all the prevalent cases before conducting the analysis.

Incident MI and stroke cases

The study population after excluding those having baseline MI or stroke events were further classified into incident MI cases, incident stroke cases and controls. Incident cases were those who had event during the median follow up time of seven years from the day of baseline assessment. The initially calculated time-to-MI-event variable was recoded into a dichotomous variable, in which positive values were coded as 1 and demonstrated as incident MI cases and missing values were recoded as 0 which depicted controls. Negative to 0 values were coded as missing values. The similar strategy was utilized to identify the incident stroke cases. Missing values were just ignored and no imputation was performed.

Statistical analysis

All the statistical analyses were performed using R v. 4.0.2 (R Foundation for Statistical Computing, Austria). The data was exported from original data base in csv file format and filtration of data was done according to the inclusion and exclusion criteria. The variables were constructed or recoded as per need of the analysis by utilizing appropriate R functions. R packages "survival", "survminer", "dplyr", "forest plot" and ggplot2" were used in analysis.

Descriptive statistics was presented in the form of mean (standard deviation) for continuous variables and as percentage for categorical variables. Association of neuroticism with incident MI and stroke was examined by one of the most popular regression techniques for survival analysis, i.e., Cox proportional hazards regression, which is used to relate several risk factors or exposures, considered simultaneously, to survival time. In present study, in a Cox proportional hazards regression model, the measure of effect is the hazard rate, which is the risk of MI or stroke given that the participant has survived up to a specific time. Time-to-event variables for MI and stroke were used as time variables and incident MI and incident stroke were used as outcome variables to conduct this analysis. Moreover, effect modification of occupational categories on this association was further investigated by stratification of study population according to occupational categories. Three models were constructed to evaluate the association while adjusting the analysis in each model with further covariates. In model I, also referred to as basic model, the analysis was adjusted for demographic characteristics (sex, age and TDI) as covariates. Further adjustments of the analysis were performed in model II in which lifestyle factors (alcohol drinking status, smoking status, and physical activity) were used as covariates in addition to model I. In model III, or fully adjusted model, analysis were further adjusted for medical history factors (hypertension, diabetes, and depression) as covariates along with those covariates that were used in model II. The results of Cox proportional hazard regression are presented as hazard

ratio (HR). If the HR is greater than one, it depicts as risk is increased, if it is less than one it shows as risk is lowered or protective effect while HR equals to one shows no effect. The significance level was set at 95% confidence interval or p value <0.05. The horizontal forest plot for visual representation of the results were also made by R v. 4.0.2 (R Foundation for Statistical Computing, Austria).

Results

The present study investigated the association between neuroticism and risk for MI and stroke in UKB cohort. The study population comprised of 375,713 participants as per exclusion criteria in study consort diagram (Figure 2). Since the present study considered the neuroticism score as the main exposure so all the participants who lacked the information regarding neuroticism score in UKB were excluded from the study . Furthermore, we also excluded the participants having MI and stroke either before or at the baseline assessment (prevalent cases) so that we could identify a clear association between neuroticism and incidence of MI and stroke. Thus, 375,713 participants without reporting any MI or stroke event at baseline assessment were included in the study while 4,459 MI and 2,322 stroke incident events were recorded during a median follow-up time of 7 years.

Descriptive statistics

The main aim of descriptive statistics was to summarize the baseline characteristics of our study population and identify the baseline exposure levels of different factors that are related with MI and stroke incidence and neuroticism. Descriptive analysis was performed to obtain the number and percentage of participants into the different levels of the categorical and dichotomous variables, as well as to calculate the mean and standard deviation for all continuous variables.

Table 1 shows the descriptive statistics of study population comprises of 375,713 participants. The study population consists of 54.47% females and 45.53% males with mean age of 56.24 (Standard deviation (SD) = 8.06) years and the mean BMI of 27.35 kg/m^2 (SD = 4.74). Moreover, the socioeconomic status of the participants is represented by the TDI (towndep index) in descriptive statistics Table 1. The negative TDI value represents high socioeconomic status while the positive TDI value represents the low SES (Tyrrell *et al.,* 2016). So it can be shown by results that average sample population belonged to high socioeconomic status as the mean TDI of sample population was found to be -1.43(SD= 3.01) . Regarding the lifestyle factors, more than half of the participants are those who have never smoked in their entire life while 34.44% were smoking previously in life resulting in 10.23% people as current smokers. The ratio of previous smokers or those who had quit smoking is remarkably higher as compared to those who are smoking currently.

A huge percentage of sample population were alcohol consumers currently and previously. The MET score is a representative variable of physical activity has mean 3065 (SD=3972) among study population. Where the medical history is concerned, 24.96% participants had high blood pressure , 4.62% were diabetic and 27.22% were suffering from depression. Around one fourth of the study population from UK Biobank is suffering from the depression and hypertension.

Stratification of the study population into occupational categories can be seen with respective frequency distribution. The occupation “managers and senior officials” and “administrative occupations” were occupations with highest number of participants of 18.12% and 15.55 % respectively. Whereas the “sales and customer service” was the occupational group that had lowest percentage of the participants with 3.36%. “Skilled occupations” was the second dominant occupation with 12.57% of population.

The frequency distribution of other occupational categories revealed that 5.11% participants belonged to “science and technology occupations, 12.36% to “associate and technical occupations”, 6.54% to “business and public service”, 6.81% to “health professionals”, 8.% to the

"operatives and elementary occupations", and 10.83% were related to "teaching and research profession".

Table 1. Baseline characteristics of UK Biobank participants. Percentages reported in the table are the valid percentage of non-missing values.

Characteristics	Frequencies (N)	Percentages (%)*	Mean ± Standard Deviation (SD)	Missing values
Study sample	375,713	100		
1. Sex				0
a. Female	204,641	54.47		
b. Male	171,072	45.53		
2.Age			56.24 ± 8.06	0
3.BMI			27.35 ± 4.74	
3. TDI			-1.43 ± 3.01	456
4. Smoking				978
a. Never	207,350	55.33		
b. Previous	129,043	34.44		
c. Current	38,342	10.23		
5. Alcohol intake				161
a. Yes	360,697	96.04		
b. Never	14,855	3.95		
6. Physical activity (MET Score)			3065 ± 3972	
7. Hypertension				9,084
a. Yes	91,546	24.96		
b. No	275,083	75.03		
8. Diabetes				636
a. Yes	17,314	4.62		
b. No	357,763	95.38		
9. Depression				280,073
a. Yes	26,029	27.22		
b. . No	69,611	72.78		
10.Occupations				136,287
1. Science and Technology	12,221	5.11		
2. Administrative Occupations	37,251	15.55		
3. Associate and Technical Occupations	29,603	12.36		
4. Business and Public Service	15,681	6.54		
5. Health Professionals	16,310	6.81		

6.	Machine Operatives and Elementary Occupations	20,875	8.71
7.	Managers and Senior Officials	43,402	18.12
8.	Sales and Customer Service	8,048	3.36
9.	Skilled Occupations	30,107	12.57
10.	Teaching and Research	25,928	10.83

Association between neuroticism and MI incidence

The association between neuroticism and risk of MI incidence has been observed in the study population of UKB. Cox proportional hazard regression was performed to evaluate the association between 1-SD increase in neuroticism score and the incidence of MI. . The final time-to-MI-event were used as time variables, whereas the incident MI cases variables were used as the outcome variable in the respective analysis. (Figure 2A). Three models were built to adjust the analysis for different covariates. Covariates are related with both the predictor and the health-related outcomes, which can lead to spurious associations if not controlled. Adjusting the analysis for those covariates, their effects are controlled, which result to the identification of the real association of neuroticism with MI incidence

The result of this relationship between risk of incident MI and 1-SD increase in neuroticism score is shown in Figure 2 A. The increase in 1-SD in neuroticism had a 1.103 fold increased risk for MI (HR : 1.103, 95% CI: 1.070-1.136) in model I which was adjusted for demographical covariates such as age, sex, BMI and TDI. . The risk for MI was slightly attenuated but still remains statistically significant with HR: 1.086 (95 % CI: 1.050-1.124) when further adjustment of model I was made to life style factors such as alcohol, smoking and physical activity in for the model II . The association has been persistently significant in all the models used and remained statistically significant in fully adjusted model that is model III after further adjustment with medical history covariates which are hypertension, diabetes and depression with HR: 1.047(1.009-1.087)after controlling for all the confounding factors. (Figure 2A).

Association between neuroticism and stroke incidence

The association between neuroticism and risk of stroke incidence has been observed in the study population of UKB. Cox proportional hazard regression was performed to evaluate the association between 1-SD increase in neuroticism score and the incidence of stroke. . The final time-to stroke-event were used as time variables, whereas the incident stroke cases variables were used as the outcome variable in the respective analysis. (Figure 2B). Three models were built to adjust the analysis for different covariates. Covariates are related with both the predictor and the health-related outcomes, which can lead to spurious associations if not controlled. Adjusting the analysis for those covariates, their effects are controlled, which result to the identification of the real association of neuroticism with stroke incidence.

The result of this relationship between risk of incident stroke and 1-SD increase in neuroticism score is shown in Figure 2 B. The increase in 1-SD in neuroticism had a 1.03 fold increased risk for stroke(HR: 1.025, 95% CI: 0.985-1.066). in model I which was adjusted for demographical covariates such as age, sex, BMI and TDI. However when the model I was further adjusted for life style factors such as alcohol, smoking and physical activity in model II this association became statistically insignificant. This insignificance remained present when the model II was further

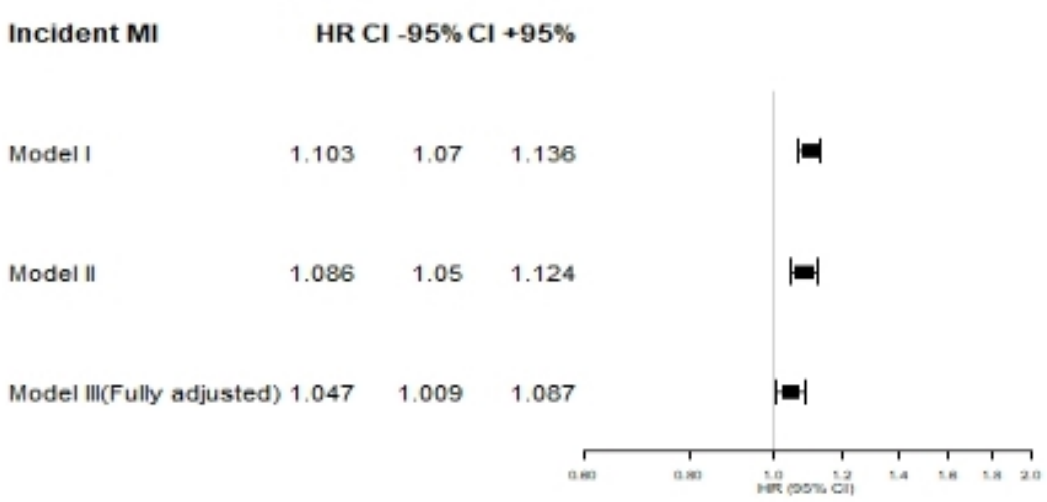
adjusted with medical history factors such as hypertension, diabetes and depression in model III (Figure 2B).

Association between neuroticism and combined MI and stroke incidence

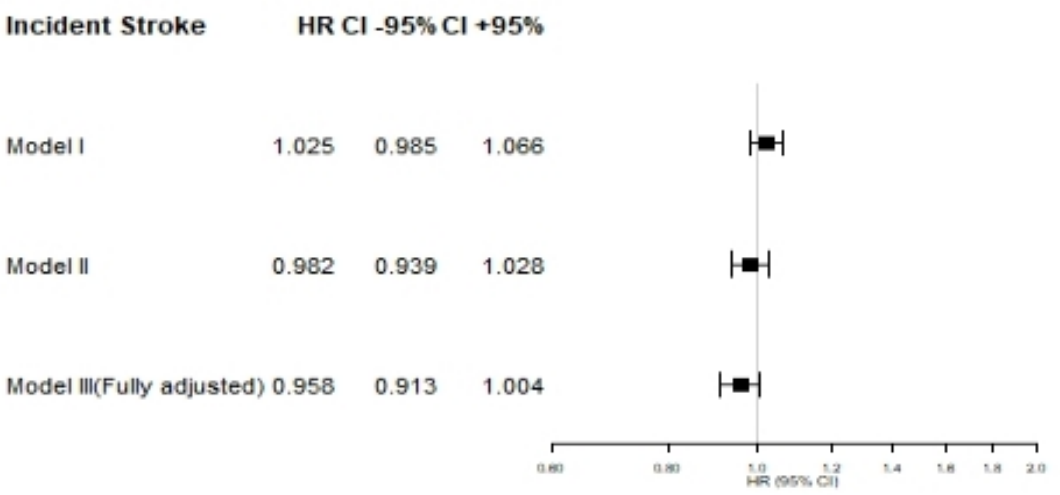
The association between neuroticism and risk of stroke and MI incidence has been observed in the study population of UKB. Cox proportional hazard regression was performed to evaluate the association between 1-SD increase in neuroticism score and the incidence of stroke and MI. Time-to-MI and stroke event variable was used in the analysis. The corresponding R function was used to construct the variable so that whichever event occurred first, that event should be considered. whereas the incident stroke and MI cases variables were used as the outcome variable in the respective analysis. (Figure 2C). Three models were built to adjust the analysis for different covariates. Covariates are related with both the predictor and the health-related outcomes, which can lead to spurious associations if not controlled. Adjusting the analysis for those covariates, their effects are controlled, which result to the identification of the real association of neuroticism with stroke and MI incidence.

The association between combined hazard ratio of risk of incident MI and stroke and 1-SD increase in neuroticism score was demonstrated in figure 2C. The hazard ratio for combined risk of MI and stroke was found to be significant with 1.075 folds increased risk for MI and stroke incidence. (HR : 1.075, 95% CI : 1.050-1.101) in model I which was adjusted for demographical covariates (Age, Sex, BMI and TDI). The association between combined hazard ratio of risk of incident MI and stroke and 1-SD increase in neuroticism score has been persistently significant in model II which was further adjustment of model I with factors (alcohol, smoking and physical activity) HR: 1.051 (1.023-1.081). When the final adjustment was made by further adjustment of model II for the medical history covariates such as (Hypertension, Diabetes, Depression) the HR for risk of MI and stroke incidence associated with 1-standard deviation SD increase in neuroticism score became statistically insignificant, (Figure 2C)

A



B



C

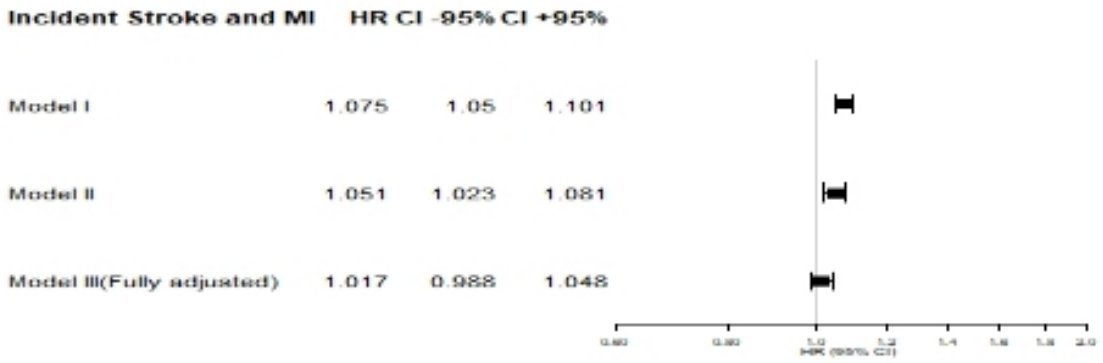


Figure 2. Forest plot showing the Cox proportional adjusted hazard ratios (HR) for MI and Stroke incidence associated with 1-Standard Deviation increase in neuroticism score. Cox regression analysis was adjusted for different covariates. Model I was adjusted HR for demographic characteristics (age, gender and TDI) as covariates. Model II: Model I + lifestyle factors (alcohol drinking status, smoking status and physical activity) as covariates, Model III (Fully adjusted model): Model II + Medical history (Hypertension, Diabetes, Depression) as covariates. CI -95% CI +95% are lower and upper level of 95% confidence interval respectively. A: Forest plot showing association between MI and with 1-Standard Deviation increase in neuroticism score. B: Forest plot showing association between stroke and with 1-Standard Deviation increase in neuroticism score. C: Forest plot showing association between MI and stroke and with 1-Standard Deviation increase in neuroticism score. (MI=Myocardial infarction, HR= Hazard ratio, -95%CI: lower limit of 95% confidence interval, +95%CI: upper limit of 95% confidence interval)

Association between neuroticism and MI incidence, stroke incidence among occupational categories

To evaluate the association between neuroticism and incident MI or stroke across the different occupational categories, the study population was stratified according to respective occupations

while conducting the cox-proportional regression analysis in fully adjusted model as shown in Table 2. Covariates are related with both the predictor and the health-related outcomes, which can lead to spurious associations if not controlled. Adjusting the analysis for those covariates, their effects are controlled, which result to the identification of the real association of neuroticism with stroke and MI incidence.

The model III or fully adjusted model where adjustment for demographic covariates (age, gender and TDI) , lifestyle factors (alcohol drinking status, smoking status and physical activity) and medical history (hypertension, diabetes, depression) has been made to observe the association by controlling for all the confounders and results showed no statistical significant association in any of the occupational categories. Sample population had been stratified into the ten occupational categories and none of the occupational category showed significant association for risk of MI and stroke and 1-SD increase in neuroticism score.

Table 2. Cox proportional adjusted Hazard Ratios for MI, stroke, and both stroke and MI, stratified into occupational categories in UK biobank.

	Occupations	**MI**				**Stroke**				**MI and Stroke**			
		HR	95.0% CI Lower	95.0% CI Upper	p-value	HR	95.0% CI Lower	95.0% CI Upper	p-value	HR	95.0% CI Lower	95.0% CI Upper	p-value
1	Science and Technology	1.092	0.859	1.388	0.474	1.062	0.758	1.488	0.727	1.088	0.895	1.324	0.396
2	Administrative Occupations	1.053	0.905	1.226	0.505	0.908	0.754	1.095	0.314	0.988	0.878	1.111	0.836
3	Associate and Technical Occupations	0.990	0.857	1.144	0.888	0.963	0.779	1.190	0.726	0.986	0.874	1.111	0.815
4	Business and Public Service	1.098	0.899	1.340	0.359	1.094	0.867	1.380	0.450	1.101	0.947	1.282	0.211
5	Health Professionals	0.959	0.711	1.292	0.783	0.800	0.563	1.138	0.215	0.888	0.707	1.116	0.309
6	Machine Operatives and Elemantry Occupations	0.957	0.826	1.109	0.557	0.914	0.735	1.136	0.419	0.950	0.841	1.073	0.408
7	Managers and Senior Officials	1.022	0.906	1.152	0.724	0.868	0.728	1.035	0.115	0.975	0.883	1.077	0.620
8	Sales and Customer Service	0.973	0.757	1.252	0.833	1.172	0.819	1.677	0.387	1.051	0.855	1.292	0.635
9	Skilled Occupations	1.084	0.947	1.240	0.241	1.077	0.896	1.295	0.431	1.073	0.962	1.197	0.207
10	Teaching and Research	0.953	0.780	1.165	0.641	0.908	0.725	1.137	0.401	0.941	0.810	1.094	0.432

MI: myocardial infarction, HR: hazard ratio, CI: confidence interval,

Discussion

This prospective population-based cohort study of 375,713 individuals from UK examined the association between neuroticism and future risk of MI and stroke over a follow up period of seven years. The follow up period was chosen to be seven years based on the data available because last reported case of incident MI was in year 2016. We believe if the followup would be extended to longer period then more case might be reported and results might be different.

High neuroticism was associated with an increased future risk of MI and this association remained significant after controlling for confounders such as demographics, lifestyle factors and health

profiles. However, no significant association was observed between neuroticism and stroke as well as between neuroticism and overall CVD (MI and stroke combined). Moreover, no significant association was observed between neuroticism and MI/stroke/overall CVD after stratification into the occupational categories.

In agreement with our findings, a U.S cohort study of 1,255 participants (where the baseline structural equation has been presented) revealed significant paths from neuroticism to heart rate variability (HRV, CVD and depression and concluded that neuroticism has independent associations with both autonomic reactivity and CVD, over and above its associations with depression and other related variables. If we take into account this study with purpose to understand the mechanism behind the interaction of neuroticism and CVD, this study suggested that neuroticism could account for portions of the phenotypic association of HRV with CVD, and depression (Čukić *et al.,* 2015).. The neuroticism in the study by Čukić *et al* was assessed using an adjective-rating scale derived from existing Big Five trait lists and inventories . The adjectives were: "moody", "worrying", "nervous" and "calm" and participants rated themselves on each item using a Likert scale ranging from 1: "Not at all" to 4: "A lot" while in present study neuroticism score is an externally derived summary score that covers twelve domains of neurotic behaviors and was assessed via touchscreen questionnaire. This 12-item personality questionnaire is known as Eysenck Personality Questionnaire-Revised Short Form and considered as valid and reliable (Eysenck *et al*., 1985).

Several mechanisms may explain this link between psychological factors, personality traits and bad health outcomes such as CVD. These factors may include some genetic predisposition, rather poor lifestyle a person, poor compliance to health care recommendations, and direct pathophysiologic perturbations. The latter may include changes in the hypothalamic-pituitary adrenal axis and autonomic dysfunction which may result in endothelial dysfunction and inflammation. (Von *et al.,* 2012).

Moreover, personality traits may have an effect on cardiac physiology as well stated by the study revealing that ECG amplitude patterns are correlated with the personality of an individual and further explained human personality has brain correlates that has profound effect on biological processes. One study investigated relations between emotional personality and heart activity and concluded that emotional personality is related to a specific cardiac amplitude signature in the resting electrocardiogram (ECG). Two experiments in this study by using magnetic resonance imaging showed that this signature correlates with brain activity in the amygdala and the hippocampus during the processing of musical stimuli. Additionally, this cardiac signature also found to be correlated with subjective indices of emotionality such as personality type and with both time and frequency domain measures of the heart rate variability. The results demonstrated complex connections between emotional personality and the heart by showing that ECG amplitude patterns provide considerably more information about an individual's emotionality than previously believed (Koelsch *et al.,* 2012).

Apart from association with MI, higher neuroticism was associated with an increased risk of stroke incidence in age and gender-adjusted models. However, after controlling for lifestyle factors such as smoking and alcohol consumption status, physical activity, and medical conditions such as hypertension, diabetes and depression, neuroticism was no longer associated with future risk of incident stroke. These results suggest that physiological factors and medical history did mediate the association between neuroticism and stroke. The results in perspective of incident stroke might be comparable with another population-based cohort study with 9-year follow-up with 2,050 participants having ages more than 55 years while containing 52% female as participants. The incidence of stroke was determined by self-report data in that study as well as data from general practitioners and death certificates. Neuroticism was measured using the Dutch Personality . As a result of Cox proportional hazards regression.' it was seen that in persons without preexistent cardiac disease, depression is only predictive for future stroke in absence of high neuroticism (Marijnissen *et al.,* 2014). Whereas the association of neuroticism with overall

increased risk for altogether MI and stroke incidence is concerned, the association was found after controlling the demographics (age, sex, BMI, socioeconomic status) and lifestyle confounders (smoking status, alcohol consumption and physical activity). However, after adding the measure of medical history such as hypertension, diabetes and depression in the fully adjustment, this association was attenuated and became non-significant. These findings strongly indicate the mediating effect of confounders in CVD risk associated with neuroticism which does make this domain more dynamic to draw some definite conclusion regarding direct interaction between personality and health outcomes. These findings are consistent with a previous study, which found that neuroticism was a risk factor for mortality in a community sample but that this relationship did not remain significant after controlling for several health and behavioral predictors (Wilson *et al.,* 2005).

In addition a study including 800 elderly female and male clergy in a 5-year longitudinal design also found that participants who had high neuroticism scores observed to have approximately double the death rate as compared to those with low neuroticism scores (Wilson *et al.,* 2004). Apart from the lifestyle and socioeconomic factors, there can be a possibility of certain psychological factors to mediate this association too as Maier *et al* proposed one possible interpretation that the effect of neuroticism on mortality is mediated via low mood (depressed states) or other psychiatric illness, which also associate with mortality (Maier *et al.,* 1999). There is another study that suggests that in older depressed persons without a history of diagnosed vascular disease, persons with a low level of neuroticism have a higher risk of developing stroke, compared to those with a high level of neuroticism (Marijnissen *et al.,* 2014). However in contrast to this a longitudinal study of 65- to 100-year-old participants concluded that higher neuroticism did not predict mortality in sample population (Weiss et al., 2005).

Psychosocial risk factors have direct pathophysiologic effects but also influence life style and behavior Various stress management intervention programs have proven to be effective. Psychosocial intervention in conjunction with cardiac rehabilitation programs has shown to reduce cardiovascular morbidity and mortality. Stress is a reaction of the organism to a stressor with various negative health consequences including the development of arteriosclerosis. Stress may cause myocardial ischemia, rhythm disturbances, platelet stimulation, increased blood viscosity through hemoconcentration as well as endothelial dysfunction and coronary vasoconstriction in the presence of arteriosclerosis of the coronary arteries. Psychosocial risk factors may also lead to the development and to clinical consequences of arteriosclerosis. (Saner et al., 2008)

Moreover, in present study when the study population was stratified according to occupational categories the association between neuroticism and MI becomes non-significant. We could not nominate any specific occupation being a high-risk occupation for CVD in context of neuroticism. One possibility could be the lowering of sample size across occupational categories might have resulted in lower statistical power. Future investigations using larger data and taking into consideration the working environment such as length of working hours, nature of work, physical activity involved in specific occupation, working place environment and interaction with colleagues, salary satisfactions and other such factors are needed to accept or refute these findings. Current study results are not that comparable with previous work as our study had focused on cardiovascular studies and previously two prominent studies which focused the association of neuroticism with mental and physical disorders revolved around emergency personnel and police officers The sample used for this study comprised 1,535 police officers from a British police force among which 20.78 per cent of were female and it explored the relationships among covariates , such as gender, age, rank, tenure and personality, occupational stress, coping strategies, well-being, organizational commitment and job satisfaction and concluded that neuroticism was found to be significantly and positively related to perceived sources of stress such as perceiving bureaucracy and politics and inter-personal conflicts as stressful. (Ortega *et al.,* 2005). Another interesting study that was conducted to assess whether neuroticism has a negative or positive impact on subjective and objective health and health

behaviours in emergency personnel. For this study, cross-sectional UK Biobank baseline data of emergency personnel (police, firemen and paramedics) was used and an interesting positive and negative associations between neuroticism and health outcomes and behaviours was observed as high neuroticism was positively associated with poorer subjective health outcomes in all emergency personnel however the neuroticism in firemen was associated with reduced abdominal obesity and increased exercise (Mutambudzi et al., 2020).

The evidences of relationship between cardiovascular diseases with working environmental factors such as working hours are available in previous study such as Kivimäki et al stated that employees who work long hours have a higher risk of stroke than those working standard hours however the association with coronary heart disease is weaker (Kivimäki et al., 2015). Workplace stress has been under consideration in policy making authorities of many countries. Such as the Italian law requires all companies, including the police, to assess the risk of work-related stress through systematic collection of information, the so-called 'objective indicators of stress', that refer to factors of job description such as workload and work schedule as well as working environment factors like autonomy, and interpersonal conflict within the organization (Garbarino et al., 2018) But in some cases. Due to limited interventional evidence on benefits, harms and cost-effectiveness, definitive recommendations have not been made for the primary prevention of cardiovascular disease via workplace stress reduction. Nevertheless, governments are already launching healthy workplace campaigns, and preventing excessive work stress is a legal obligation in several countries. Promoting awareness of the link between stress and health among both employers and workers is an important component of workplace health promotion (Kivimäki et al., 2015)

Indeed it is evident that the prevention of cardiovascular disease should not only focus on pathophysiological risk factors or to the measurement of certain blood-values and treatments. Efforts must also go into creating the conditions for a healthier life and promote possibilities for healthier behavior. Appropriate screening for psychosocial traits and personality assessment should be part of the standard history (Meier *et al.,* 2005). The most effective psychosocial treatment should be multicomponent therapy that combines elements of cognitive behavior therapies such as stress management, personality trait assessment such as neuroticism and changes in health behaviors, including the adoption of a regular exercise regimen and healthy life style. . Gender-specific issues should probably be considered. In this way this study has opened new insight into the field of behavioral cardiology by accumulating a wealth of epidemiological, mechanistic and clinical knowledge that undoubtedly has furthered our understanding about the important role of psychosocial risk factors in patients with a heart disease.

When it comes the novelty of the present work it can be seen that the previous literature regarding association between neuroticism and CVD is very multi-directional as most of the studies focused on the participants with particular health condition such as depressed people (Almas *et al.,* 2017) or specific age group and certainly one gender (Johnson *et al.,* 2012). However, the present study, to the best of our knowledge, is the first study to investigate the association between neuroticism and MI and stroke without stratification for health conditions or other factors in the overall population and with the largest sample size so far which made it distinguished among others. Apart from the higher statistical power, it is also important to note differences between our analytic strategy and a previous reported study. Such as study from the HALS study (Shipley *et al.,* 2007) showing that neuroticism was associated with all-cause and CVD mortality for both sexes and all ages combined but not when the sample was divided into age groups and the estimate was adjusted for health behaviors and physiological variables. The results of both studies are not comparable because the HALS study focused on mortality whereas the present study assesses the risk of incidence of MI and stroke due to high neuroticism. It is very important to notice that the present study is focused on incidence of CVD not the mortality associated with CVD.

Another population-based prospective cohort study in Japan also does not support the hypothesis that personality is a risk factor for mortality from Ischemic heart disease (IHD) and stroke. In this Japanese study, 41,442 residents of Miyagi Prefecture in northern Japan completed the Japanese version of the short-form Eysenck Personality Questionnaire-Revised and another questionnaire on various health habits and followed up for 11 years. Cox regression was applied to estimate the relative risk of IHD and stroke and no association of stroke and IHD was found with neuroticism(Nakaya *et al.,* 2005). The findings of this Japanese study is much in agreement with our findings in UKB where no significant association was found between stroke and neuroticism.. Batty et al., 2015 also reported the negative association between neuroticism and CVD (Batty *et al.,* 2015).

So, the present study is an important contribution in understanding this dynamic domain of understanding the health outcomes of neuroticism in context with some previous studies.

There are several strengths of the present study that need to be acknowledged. Firstly, the study used large sample size reflecting higher statistical power. High statistical power not only increases the accuracy of the estimations but also the generalizability of the results as having sufficient participants in each group as cases and control makes the results more generalized (Kukull *et al.,* 2012). Secondly, the longitudinal design and the use of a population-based sample in this study makes it more accurate epidemiological study. The validated instruments for assessing CVD factors (MI and stroke) and neuroticism in UKB does make the results more reliable. Moreover, the participants with CVD at baseline were excluded to prevent misclassification of outcome and incident MI and stroke cases were identified through hospital records and death registries, which makes the data and this longitudinal association more reliable. Lastly, to prevent bias in study, the analyses were adjusted for a high number of confounding covariates that could be potential mediators of outcome if not controlled for. Apart from the strengths of the study, the present study should also be assessed in light of certain limitations as well as most of the lifestyle factors data used in the study was self-reported and self-reported information may lead to information bias if not reported correctly (Ekström *et al.,* 2015).

Additionally, the high number of missing values in some of the variables used in the analysis might have affected the precision and significance of the results and could potentially cause bias.

Ethical aspects, gender perspectives, and impact on the society

The data for the present study has been extracted from the UKB cohort. The UK Biobank study was approved by the North West multicentre ethics research committee. The participants in the study provided written informed consent for data collection and analysis. UKB has the ethics and governance framework (EGF) and possesses a "Human Tissue Authority" licence. The current project has been conducted using the UKB resource under application number 25308. In the present study, all investigations have been conducted in accordance with the tenets of the EGF of UK biobank that sets standards for the UKB projects so that all necessary safeguards are in place to ensure that the data and samples are only used for scientifically and ethically approved research. No further ethical approval was required as no personal information or contact with the participants were intended in the study. The identity of the participants was unknown while performing the analysis. No known conflicts of interests were identified in the performance of this study. All data processing and analysis tools were freely available as open source. Results and derived conclusions are completely based on the clinical data originated from the UKB and strictly in the perspective of clinical significance and research-based importance. The results in the study gives possible supporting information about association of high neuroticism with incidence of MI risks

The gender perspective of the study has also been taken into consideration as gender was used as covariates in model . For example gender analysis in risk factors and prevention reveals that the harmful effects of tobacco smoke on atherosclerosis are greater in women than in men (Risè et al., 2010) so it is very important to take into consideration the gender perspectives while

conducting research for assessment of clinical risk factors as it may have potential impact both in quality of life and well being of both men and women in society equally and differently. The present study may impact the society by stratifying the population according to their individual personality and give an insight that this individual society can predict their cardiac health outcomes. It may give a scope of health care policy makers to make such application or strategies that improve the quality of life of people by taking into consideration their personality traits assessment as raising a problem is not worthy without proposing the solution of this problem.

Future perspectives

To our knowledge, this is the first study which investigated the association of neuroticism with risk of MI and stroke incidence with a big sample size. Our findings highlight that the people with high neuroticism are risk group for MI and opens further directions for future research. These findings open new perspectives for more efficient risk stratification and pre-clinical diagnosis of individuals at risk for MI depending upon their neuroticism profiles and in turn open the ways to reduce the disease burden and health care budget consumption. Appropriate screening for psychosocial traits and personality assessment should be part of the standard history (Meier et al., 2005). Early screening of people with high neuroticism and developing preventive strategies can be investigated further to assess whether it mediates the outcome or not. The same association can be further evaluated by taking into consideration healthy lifestyle factors such as physical activity and diet intake and assess that how those mediate the effects. Indeed further studies are required to see how this MI risk can be reduced by implementing appropriate preventive measures and healthy life style.

The future directives of this research question or domain should be focussed on two aspects. Firstly, it is very important to explore or investigate the origin or mechanism with which neuroticism impacts the health outcomes and one option is to investigate the exogenous factors involve in this interaction. To explore the relationships among exogenous factors, such as gender, age, life style covariates, socioeconomic factors personality and occupational stress some future research hypothesis should be formed by utilizing modern statistical analysis. Structure equation modelling (SEM) is such a tool to assess the correlation and interaction between these exogenous factors (Čukić et al., 2015). Secondly, the assessment of coping strategies in response to the stressors should done by formulating a comprehensive questionnaire. This may help in providing the behavioral therapies to the high neurotic who are at risk poor health outcomes. Ortega et al suggested that coping strategies choices of an individual can be one of following such as developing a plan of action, socializing, discussing the problem, ignoring, or moaning and grouching. (Ortega et al., 2006)

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References

Almas, A., Moller, J., Iqbal, R., & Forsell, Y. (2017). Effect of neuroticism on risk of cardiovascular disease in depressed persons - a Swedish population-based cohort study. BMC cardiovascular disorders, 17(1), 185. https://doi.org/10.1186/s12872-017-0604-4

Aguinis, H., Gottfredson, R. K., & Joo, H. (2013). Best-practice recommendations for defining, identifying, and handling outliers. Organizational Research Methods, 16, 270– 301. DOI: https://doi.org/10.1177/1094428112470848

Barberi, C., & van den Hondel, K. E. (2018). The use of cardiac troponin T (cTnT) in the postmortem diagnosis of acute myocardial infarction and sudden cardiac death: A systematic review. *Forensic science international*, *292*, 27-38. Batty, G. D., Jokela, M., Kivimaki, M., & Shipley, M. (2016). Examining the long-term association of personality with cause-specific mortality in London: Four decades of mortality surveillance in the original Whitehall Smoking Cessation Trial. *American journal of epidemiology*, *184*(6), 436-441.

Benavides FG, Benach J, Diez-Roux AV. (2000) How do types of employment relate to health indicators? Findings from the Second European Survey on Working Conditions. Journal of Epidemiology & Community Health 2000;54:494-501.

Benyamini, Y., Idler, E. L. (1999). Community studies reporting association between self-rated health and mortality: Additional studies, 1995 to 1998. Research on Aging, 21, 392–401. doi:10.1177/0164027599213002

Chida Y, Steptoe A. (2009) The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. J Am Coll Cardiol. 2009;53(11):936–946. doi: 10.1016/j.jacc.2008.11.044.

Chiorri C, Garbarino S, Bracco F, Magnavita N. (2015). Personality traits moderate the effect of workload sources on perceived workload in flying column police officers. Front Psychol 2015;6:1835.

Chiorri, C., Garbarino, S., Bracco, F., & Magnavita, N. (2015). Personality traits moderate the effect of workload sources on perceived workload in flying column police officers. Frontiers in psychology, 6, 1835.

Costa PT, McCrae RR. (2008), The revised neo personality inventory (neo-pi-r). The SAGE handbook of personality theory and assessment. London: Sage Publications; 2008;2:179–98.

Costa, P. T., Weiss, A., Duberstein, P. R., Friedman, B., Siegler, I. C. (2014). Personality facets and all-cause mortality among Medicare patients aged 66 to 102 years: A follow-on study of Weiss and Costa (2005). Psychosomatic Medicine, 76, 370–378. doi:10.1097/PSY.0000000000000070

Cuijpers, P., Smit, F., Penninx, B. W., de Graaf, R., ten Have, M., Beekman, A. T. (2010). Economic costs of neuroticism: A population-based study. Archives of General Psychiatry, 67, 1086–1093. doi:10.1001/archgenpsychiatry.2010.130

Čukić, I., & Bates, T. C. (2015). The association between neuroticism and heart rate variability is not fully explained by cardiovascular disease and depression. *PloS one*, *10*(5), e0125882.

Esquirol, Y., Perret B., Ruidavets, J.B. (2011). Shift work and cardiovascular risk factors: new knowledge from the past decade. Arch Cardiovasc Dis. 2011 Dec;104(12):636-68. doi: 10.1016/j.acvd.2011.09.004. Epub 2011 Nov 21.

Ekström, S., Kull, I., Nilsson, S., & Bergström, A. (2015). Web-based self-reported height, weight, and body mass index among Swedish adolescents: a validation study. Journal of medical Internet research , 17 (3), e73.

Eysenck S. B. G, Eysenck H. J, Barrett P (1985). A revised version of the psychoticism scale, Personality and Individual Differences, 6:21–29.

Foong, H.F., Hamid, T.A., Ibrahim, R. and Haron, S.A. (2018), Mediating role of neuroticism in the association between loneliness and cognitive function among community-dwelling older adults. Australas J Ageing, 37: 283-287. doi:10.1111/ajag.12555

Friedman, H. S. (2000). Long-term relations of personality and health: Dynamisms, mechanisms, tropisms. Journal of Personality, 68, 1089–1107. doi:10.1111/1467-6494.00127

Gale, C. R., C ˇukic´, I., Batty, G. D., McIntosh, A. M., Weiss, A., & Deary, I. J. (2017). When is higher neuroticism protective against death? Findings from UK Biobank. Psychological Science, 28, 1345–1357. doi:10.1177/0956797617709813

Ganster, Daniel, & Rosen, Christopher (2013). Work Stress and Employee Health A Multidisciplinary Review. Journal of Management. 39. 1085-1122. 10.1177/0149206313475815.

Hagger-Johnson, G., Roberts, B., Boniface, D., (2012). Neuroticism and cardiovascular disease mortality: socioeconomic status modifies the risk in women (UK Health and Lifestyle Survey). Psychosomatic Medicine. 2012 Jul-Aug;74(6):596-603. DOI: 10.1097/psy.0b013e31825c85ca.

Hintsanen, M., Hintsa, T., Widell, A., Kivimäki, M., Raitakari, OT, & Keltkangas-Järvinen, L. (2011). Negative emotionality, activity, and sociability temperaments predicting long-term job strain and effort – reward imbalance: A 15-year prospective follow-up study. *Journal of psychosomatic research* , *71* (2), 90-96.

Hills, H., & Norvell, N. (1991). An examination of hardiness and neuroticism as potential moderators of stress outcomes. Behavioral Medicine, 17(1), 31-38.

Hosmer, D. W., & Lemeshow, S. (1992). Confidence interval estimation of interaction. *Epidemiology*, 452-456.

Judge, T. A., Heller, D., & Mount, M. K. (2002). Five-factor model of personality and job satisfaction: A meta-analysis. *Journal of applied psychology*, *87*(3), 530.

Jokela M, Pulkki-Raback L, Elovainio M, Kivimaki M. (2014) Personality traits as risk factors for stroke and coronary heart disease mortality: pooled analysis of three cohort studies. J Behav Med. 2014;37(5):881–889. doi: 10.1007/s10865-013-9548-z

Jokela, M., Batty, G. D., Nyberg, S. T., Virtanen, M., Nabi, H., Singh-Manoux, A., Kivimaki, M. (2013). Personality and all-cause mortality: Individual-participant meta-analysis of 3,947 deaths in 76,150 adults. American Journal of Epidemiology, 178, 667–675. doi:10.1093/aje/kwt170

Kleppa, E., Sanne, B., & Tell, G. S. (2008). Working overtime is associated with anxiety and depression: the Hordaland Health Study. Journal of occupational and environmental medicine, 50(6), 658-666.

Kivimäki, M., & Kawachi, I. (2015). Work stress as a risk factor for cardiovascular disease. Current cardiology reports, 17(9), 74.

Karasek, R., Baker, D., Marxer, F.(1981). Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men. Am J Public Health. 1981 Jul;71(7):694-705.

Keil, U., Liese, A. D., Hense, H. W., Filipiak, B., Döring, A., Stieber, J., & Löwel, H. (1998). Classical risk factors and their impact on incident non-fatal and fatal myocardial infarction and all-cause mortality in southern Germany: results from the MONICA Augsburg Cohort Study 1984–1992. European heart journal, 19(8), 1197-1207.)

Kivimäki M, Virtanen M, Vartia M et al. (2003). Workplace bullying and the risk of cardiovascular disease and depression. Occup Environ Med. 2003 Oct;60(10):779-83.

Knol, M. J., van der Tweel, I., Grobbee, D. E., Numans, M. E., & Geerlings, M. I. (2007). Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *International journal of epidemiology*, *36*(5), 1111-1118.

Koelsch, S., Enge, J., & Jentschke, S. (2012). Cardiac signatures of personality. *PloS one*, *7*(2), e31441.

Korten, A. E., Jorm, A. F., Jiao, Z., Letenneur, L., Jacomb, P. A., Henderson, A. S., . . . Rogers, B. (1999). Health, cognitive, and psychosocial factors as predictors of mortality in an elderly community sample. Journal of Epidemiology & Community Health, 53, 83–88. doi:10.1136/jech.53.2.83

Kukull, W. A., & Ganguli, M. (2012). Generalizability: the trees, the forest, and the low-hanging fruit. *Neurology*, *78*(23), 1886–1891. https://doi.org/10.1212/WNL.0b013e318258f812

Lahey, B. B. (2009). Public health significance of neuroticism. American Psychologist, 64(4), 241.

Meier Ch, Ackermann-Liebrich U. (2005). Soziale Schicht als kardiovaskulärer Risikofaktor [Socioeconomic class as a risk factor for cardiovascular diseases]. Ther Umsch. 2005 Sep;62(9):591-5. German. doi: 10.1024/0040-5930.62.9.591. PMID: 16218492.

Maier, H., & Smith, J. (1999). Psychological predictors of mortality in old age. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *54*(1), P44-P54.

Malouff JM, Thorsteinsson EB, Schutte NS.(2006) The five-factor model of personality and smoking: a meta-analysis. J Drug Educ. 2006;36(1):47–58. doi: 10.2190/9EP8-17P8-EKG7-66AD.

Marijnissen, R. M., Wouts, L., Schoevers, R. A., Bremmer, M. A., Beekman, A. T., Comijs, H. C., & Voshaar, R. C. O. (2014). Depression in context of low neuroticism is a risk factor for stroke: a 9-year cohort study. Neurology, 83(19), 1692-1698. Mechanic OJ, Grossman SA. Acute Myocardial Infarction. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459269/

Möller-Leimkühler, A. M. (2007). Gender differences in cardiovascular disease and comorbid depression. Dialogues in clinical neuroscience, 9(1), 71.

Morris PL, Robinson RG. (1995) Personality neuroticism and depression after stroke. Int J Psychiatry Med. 1995;25(1):93–102. doi: 10.2190/E25J-BCQB-BMEM-GY9F

Mutambudzi, M., Flowers, P., & Demou, E. (2019). Emergency personnel neuroticism, health and lifestyle: A UK Biobank study. Occupational Medicine, 69(8-9), 617-624.

Nakaya, N., Tsubono, Y., Hosokawa, T., Hozawa, A., Kuriyama, S., Fukudo, S., & Tsuji, I. (2005). Personality and mortality from ischemic heart disease and stroke. *Clinical and Experimental Hypertension*, *27*(2-3), 297-305.

Nascimento, B. R., Brant, L. C. C., Marino, B. C., Passaglia, L. G., & Ribeiro, A. L. P. (2019). Implementing myocardial infarction systems of care in low/middle-income countries. *Heart*, *105*(1), 20-26.Nicholas, A. ,Turianoa, B, Daniel, K . (2013) Big 5 personality traits and interleukin-6: Evidence for "healthy Neuroticism" in a US population, Behavior, and Immunity 28 (2013) 83–89

Office for National Statistics. Standard Occupational Classification. (2000). http:// www.ons.gov.uk/aboutstatistics/classifications/archived/SOC2000/index.html (accessed in Oct 2015).

Ortega, A., Brenner, S. O., & Leather, P. (2007). Occupational stress, coping and personality in the police: an SEM study. International Journal of Police Science & Management, 9(1), 36-50.

Petersen GL, Mortensen EL, Rod NH, Lange T, Flensborg-Madsen T, Hansen ÅM (2018) . Occupational social class and personality traits in relation to leisure-time physical activity level: cross-sectional results from the Copenhagen Aging and Midlife Biobank. J Aging Health,30: 1263–1283. 10.1177/0898264317714928

Verkoeijen, P., Polak, M. G., & Bouwmeester, S. (2018). A practical illustration of methods to deal with potential outliers: A multiverse outlier analysis of study 3 from Brummelman, Thomaes, Orobio de Castro, Overbeek, and Bushman (2014). *Collabra: Psychology*, *4*(1).Risè, P., Galli, C.,

Amato, M., Ghezzi, S., Frigerio, B., Castelnuovo, S., ... & Baldassarre, D. (2010). Effects of cigarette smoking on the relationship between fatty acids and subclinical atherosclerosis. In Congress of the International Society for the study of Fatty Acid & Lipids incorporating the 8. International Congress on Essential Fatty acids and Eicosanoids and the 5. PUFA in Maternal and Infant Health meeting.

Rukh, G., Dang, J., Olivo, G., Ciuculete, D. M., Rask-Andersen, M., & Schiöth, H. B. (2020). Personality, lifestyle and job satisfaction: causal association between neuroticism and job satisfaction using Mendelian randomisation in the UK biobank cohort. *Translational psychiatry*, *10*(1), 11. https://doi.org/10.1038/s41398-020-0691-3

Saner H (2005). Stress als kardiovaskulärer Risikofaktor [Stress as a cardiovascular risk factor]. *Ther Umsch*, 62(9), 597-602. German. doi: 10.1024/0040-5930.62.9.597. PMID: 16218493.

Shipley BA, Weiss A, Der G, Taylor MD, Deary IJ.(2007) Neuroticism, extraversion, and mortality in the UK health and lifestyle Survey: a 21-year prospective cohort study. Psychosom Med. 2007;69(9):923–931. doi: 10.1097/PSY.0b013e31815abf83.

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., ... & Liu, B. (2015). UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *Plos med*, *12*(3), e1001779.

Thombs, B. D., Bass, E. B., Ford, D. E., Stewart, K. J., Tsilidis, K. K., Patel, U., ... & Ziegelstein, R. C. (2006). Prevalence of depression in survivors of acute myocardial infarction. Journal of general internal medicine, 21(1), 30-38.

Tyrrell, J., Jones, S. E., Beaumont, R., Astley, C. M., Lovell, R., Yaghootkar, H., Tuke, M., Ruth, K. S., Freathy, R. M., Hirschhorn, J. N., Wood, A. R., Murray, A., Weedon, M. N., & Frayling, T. M. (2016). Height, body mass index, and socioeconomic status: mendelian randomisation study in UK Biobank. *BMJ (Clinical research ed.)*, *352*, i582. https://doi.org/10.1136/bmj.i582

Verkuil, B., Atasayi, S., & Molendijk, ML (2015). Workplace bullying and mental health: a meta-analysis on cross-sectional and longitudinal data. PloS one , 10 (8), e0135225.Vimalananda, V.G., Palmer, J.R., Gerlovin, H. et al (2015). Night-shift work and incident diabetes among African-American women. Diabetologia 58: 699. https://doi.org/10.1007/s00125-014-3480-9

von Känel, R. (2012). Psychosocial stress and cardiovascular risk-current opinion. *Swiss Medical Weekly*, *142*(0304).

Warren HR, Evangelou E, Cabrera CP et al. (2017). Genome-wide association analysis identifies novel blood pressure loci and offers biological insights into cardiovascular risk. Nat Genet. 2017 Mar;49(3):403-415. doi: 10.1038/ng.3768. Epub 2017 Jan 30.

Wang Y., Chen HJ. (2012) Use of Percentiles and *Z*-Scores in Anthropometry. In: Preedy V. (eds) Handbook of Anthropometry. Springer, New York, NY. https://doi.org/10.1007/978-1-4419-1788-1_2

Watson D, Clark LA, Harkness AR. (1994) Structures of personality and their relevance to psychopathology. J Abnorm Psychol. 1994;103(1):18–31. doi: 10.1037/0021-843X.103.1.18

Weiss, A., & Costa Jr, P. T. (2005). Domain and facet personality predictors of all-cause mortality among Medicare patients aged 65 to 100. Psychosomatic medicine, 67(5), 724-733.

Welin, C., Lappas, G., & Wilhelmsen, L. (2000). Independent importance of psychosocial factors for prognosis after myocardial infarction. *Journal of Internal Medicine* , *247* (6), 629-639.Welin, C., Rosengren, A., Wedel, H., & Wilhelmsen, L. (1995). Myocardial infarction in relation to work, family and life events. *Cardiovasc Risk Factors* , *5* , 30-38. Wilson, R. S., Krueger, K. R., Gu, L., Bienias, J. L., de Leon, C. F. M., & Evans, D. A. (2005). Neuroticism, extraversion, and mortality in a defined population of older persons. *Psychosomatic medicine*, *67*(6), 841-845.

Wilson, R. S., Mendes de Leon, C. F., Bienias, J. L., Evans, D. A., & Bennett, D. A. (2004). Personality and mortality in old age. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 59(3), P110-P116.

Wouts, L., Janzing, J. G., Lampe, I. K., Franke, B., de Vegt, F., Tendolkar, I., ... & Oude Voshaar, R. C. (2011). The interaction between cerebrovascular disease and neuroticism in late-life depression: a cross-sectional study. *International journal of geriatric psychiatry*, *26*(7), 702-710.