

Projekttitel	Dnr
Identifiering och utvärdering av riskfaktorer för hjärt- och kärlsjukdomar i arbetsmiljön med hjälp av stora kohorter (Identification and evaluation of risk factors for cardiovascular disease in the working environment with help of large cohorts)	

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1. Projektets syfte och bakgrund

Project's aim and background

Cardiovascular risk factors are many and form highly complex interactions between environment, behavioral patterns and genetics. This project aimed to clarify the underlying mechanisms and risk factors for cardiovascular diseases (CVD) and to produce comprehensive suggestions for preventive measures and paths to treatments in order to reduce CVD deaths specifically among the working population. More specifically, the project aimed to: 1) identify the risk groups for CVD in specific occupations, 2) assess how both work-related and non-work-related stressors and various lifestyle factors contribute to the development of different types of CVDs, and 3) estimate the genetic influences on the association between working conditions and types of CVDs.

Recently, the emphasis has been laid on the complex nature of association between work-related stress and the risk of CVD, as several behavioral and life-style related factors seem to interact in enhancing the risk for CVD in individuals with high job strain. There are two popular theoretical models on work stress, the effort reward imbalance model (Siegrist) and the demand-control or job strain model (Karasek) but the latter one is most commonly used. The demand-control model assesses the stress-related risk and active-passive behavioral

correlates of a job. It states that high-demand in terms of work-load and low-control over working conditions produce job strain while low-demand/high-control is beneficial to health (Karasek et al. AJP 1981). Throughout the decades, this model has been further expanded by adding social support in the model (Backe et al. Int Arch Occup Env. Heal. 2012). To measure the social and psychological job characteristics in this model, the Job Content Questionnaire (JCQ) has been used as a validated instrument for internationally comparative assessments (Karasek et al. J. Occup. Health Psychol. 1998). Aside from work stress, other work related factors such as physical environment (Johnson et al., Am. J. Public Health 1996) and other stressors such as discrimination and bullying (Kivimäke et al. Occup Env. Med. 2003) have been studied to be individually related to CVDs. Hence, there is a need for additional epidemiological studies with high power to explore the combined effects of these adverse working conditions in a large population with a wide age range.

We hypothesized that adverse working conditions and high job-related stress will affect the risk for CVD in both men and women, though the determinants of the increased risk might differ based on gender. We also expected to gain more in-depth knowledge on the confounding role of CVD-related lifestyle and clinical factors, by examining the contribution of different variables such as physical activity, sleep quality, smoking and drinking habits, comorbid diagnoses, medications use. We planned to elucidate the relationship of working conditions including psychosocial stress, physical environment, occupation, shift works, and other stressors with cardiovascular conditions using data from the LifeGene cohort (30,000 Swedish men and women aged 18-45) (Almqvist et al. Eur. J.Epidemiol 2011), EpiHealth study (22,000 Swedish men and women aged 45-75) (Lind et al.Eur J Epidemiol. 2013) and UK Biobank cohort (500,000 British men and women aged 40-69) (Sudlow et al. PloS Med. 2015). The LifeGene and EpiHealth cohorts include 60 work-related questions, while the UK Biobank includes 11 questions related to physical working environment as well as to job- and health-satisfaction. These large-scale cohorts provided us with a unique opportunity to analyze both the private and governmental sector work situation in both Sweden and UK.

2. Projektets genomförande

Project's implementation

The project has developed well during the last four years as we have published several studies and many are in the process of being published. We have studied all the factors that have been mentioned in the study plan. Following the project plan, each axis is progressing considerably. An overview of the project progress is presented in Figure 1.

Currently the project has produced ten studies in three dimensions as mentioned in the Figure 1.

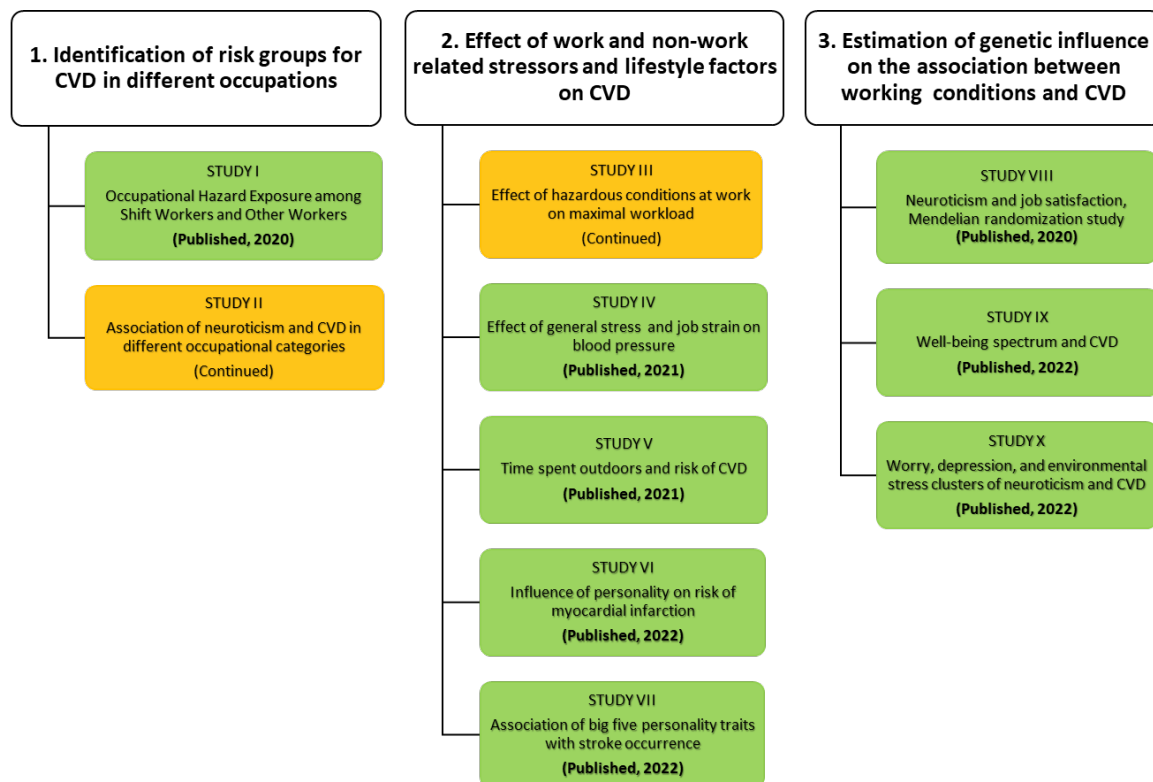


Figure 1. An overview of the project progress.

Published studies are presented in green and on going projects are presented in yellow.

Eight of these studies have already been published in well-known journals. Our study by Rukh et al. has been published in the highly rated *Translational Psychiatry* (Nature Publishing Group), (IF 5.182) (Rukh G, Dang J, Olivo G, Ciuculete D, Rask-Andersen M, Schiöth HB. “Personality, lifestyle and job satisfaction: Causal association between neuroticism and job satisfaction using Mendelian randomisation in the UK biobank cohort.” *Transl Psychiatry*. 2020). This study highlighted the relevance of using genetic instruments for studying the causal association between health parameters and both individual factors, such as personality traits and lifestyle factors including physical activity. As a result, we investigated, employing the same methodology (i.e. Mendelian Randomization) the causality between psychological factors and CVD. Our findings suggested a clear evidence for a causal association between well-being spectrum and myocardial infarction. This study has also been published in *Frontiers of Genetics* (IF 4.274) (Rukh G, de Ruijter M and Schiöth HB. “Effect of worry, depression, and sensitivity to environmental stress owing to neurotic personality on risk of cardiovascular disease: A Mendelian randomization study”). A third study was thus initiated where we evaluated the causal associations between neuroticism sub-clusters and CVD which recently published in the *Journal of Personality* (IF 5.117) (Rukh G and Schiöth

HB. “Mendelian randomization analyses for studying the effects of worry, depression and sensitivity to environmental stress owing to neurotic personality on risk of cardiovascular disease.”). These three studies have employed genetic variants to understand how personality and work environment influence the risk of developing CVD and which factors can prove to be helpful when it comes to CVD prevention.

After identifying a causal association between neurotic personality and job satisfaction, we further elaborated our work on the association between personality and CVD, and focused on analyzing all of the “Big Five” personality traits. However, only neuroticism score was readily available in the UK Biobank. Thus, we created proxies for personality traits using data from touchscreen questionnaires, which directly target the personality facets included in the Big Five Inventory. Questions on psychological factors, mental health and social support were matched to each personality trait, creating five scales scored between zero and four (sociability, diligence and curiosity) and zero and five (warmth and nervousness). These personality proxies were then used to conduct observational analyses in the UK Biobank cohort. One of our study where we have examined the longitudinal relationship between personality trait proxies and myocardial infarction has been published in *Scientific reports* (IF 4.996) (Dahlén AD, Miguet M, Schiöth HB and Rukh G. “The influence of personality on the risk of myocardial infarction in UK Biobank cohort.”). In another study we have evaluated relationship between personality traits and stroke which has been published in *Frontiers in Bioscience-Landmark* (IF 4.009) (Ruijter MJT, Dahlén AD, Rukh G, Schiöth HB. “Association of Diligence and Sociability with Stroke: A UK Biobank Study on Personality Proxies.”).

Furthermore, in order to understand which occupational categories are more vulnerable to the negative effects of personality on cardiovascular health, we investigated the association between neuroticism and CVD traits after stratifying for occupational categories (Manuscript, Shahid H, Rukh G, Miguet M, Lind L, Schiöth HB). More work is needed in this study to optimize the statistical models but this study may prove helpful in identifying risk groups for CVD in relation to occupations.

We have further investigated the maximal workload (a physical activity based test to evaluate cardiac efficiency) which is a marker of cardiovascular health in relation to physical aspects of the workplace environment. The results of this study are being summed up in a manuscript, which will soon be ready for submission (“Role of psychosocial factors in mediating the association between physical aspects of workplace environment and cardiovascular health”

Covill C, Miguet M, Rukh G, Lind L, Schiöth HB). In parallel to this work, we specifically focused on investigating the difference in the physical aspects of the workplace between shift workers and other workers. Our analysis highlighted that shift workers were not only more likely to be exposed to workplace hazards, but also to be exposed to multiple hazards at once. The study findings suggested that the physical aspects of the workplace among shift workers may contribute to their adverse health status, compared with other workers. The study has now been published in *International Journal of Environmental Research and Public Health* (IF 4.614) (Miguet M, Rukh G, Titova OE, Schiöth HB. “Important Difference between Occupational Hazard Exposure among Shift Workers and Other Workers; Comparing Workplace before and after 1980.” *Int J Environ Res Public Health*. 2020).

In another study, we investigated the association between general stress and job strain on blood pressure. The study findings supported the pivotal role of lifestyle behaviors in modulating the effect of stress on blood pressure and has now been published in *Scandinavian Journal of Public Health* (IF 3.068) (Miguet M, Olivo G, Ciuculete DM, Elmståhl S, Lind L, Schiöth HB. “Perceived stress is related to lower blood pressure in a Swedish cohort.” *Scand J Public Health*. 2021). In order to further explore the role of lifestyle factors, we investigated the relationship between time spent outdoor and risk of developing CVD. By conducting both, cross sectional and longitudinal analysis, we observed that spending more than 3.5 hours/day outdoors was associated with higher risk for myocardial infarction, even when adjusted for demographic, lifestyle and health parameters. The results of this study have been published in *Environmental Research* (IF 8.431) (Miguet M, Venetis S, Rukh G, Lind L, Schiöth HB. “Time spent outdoors and risk of myocardial infarction and stroke in middle and old aged adults: Results from the UK Biobank prospective cohort.” *Environ Res*. 2021).

To sum up, the three axis of the project have progressed well toward achieving many goals, which resulted in ten studies, eight of which have already been published, as shown in Figure 1.

3. Uppnådda resultat

General overview:

In this project, we adopted a unique approach that considered both genetic (single nucleotide polymorphisms) and non-genetic factors (lifestyle, environmental and psychological factors) to understand the risk for CVD in overall population in the context of working environment. In conclusion, our work has yielded several important results that not only filled the existing knowledge gaps to some extent but can potentially contribute to improve public health

policies in disease prevention as well as help professionals in health-related decisions. We found that improvement in working conditions over the decades has promoted safety and well-being of employs has benefitted regular-hour workers more than the shift workers who are still more exposed to occupational hazards which can explain a higher prevalence of non-communicable diseases including CVD in this population group. This finding highlights the need to pay special attention to promote occupational health specifically among shift workers (Miguet et al., *International Journal of Environmental Research and Public Health*, 2020). Second, we further support the hypothesis that lifestyle factors partially mediate the association between job-related stressors and blood pressure (CVD risk factor) (Miguet et al., *Scandinavian Journal of Public Health*, 2021).

Personality is a strong determinant for several health-related behaviours and has previously been linked to the development of cardiovascular diseases. However, the reports of personality's mediating role have been inconsistent with no data available from large population-based cohorts. We found that people with higher level of neuroticism (a personality trait that is more prone to stress and worry) suffer more from job dissatisfaction that in turn effect their efficiency and productivity. However, promoting healthier habits such as physical activity increase job satisfaction suggesting that implementing physical activity programs/ incentives may greatly benefit health of the employs and overall productivity of the organizations (Rukh et al., *Translational Psychiatry*, 2020). In further studies we found that Individuals with higher levels of diligence and sociability may be at a reduced risk of developing stroke. The potential protective effects of diligence and sociability were not fully explained by health or lifestyle factors alone. Clarifying which particular facets of conscientiousness and extraversion may influence the risk of stroke, could improve support programs and help to reduce the devastating effects of stroke (de Ruijter et al., *Frontiers in Bioscience*, 2022). Furthermore, we found influence of personality on the risk of myocardial infarction in UK Biobank cohort (Dahlen et al., *Scientific Reports*. 2022). Persons with higher levels of diligence and sociability mimicking predominantly conscientiousness and extraversion personalities respectively are less likely to experience myocardial infarction, while personalities predominantly characterised by nervousness pose higher risk for developing myocardial infarction (Dahlen et al., *Scientific Reports*. 2022). These studies highlight the importance of accounting for factors for personality that are in general very easy to measure when performing studies relating to work related factors and CVD. The novel approach we used shows great potential to be applied to other disease areas within the large-scale UKB population to increasingly characterise how personality can both predispose and protect against specific illnesses. This will in turn help to develop individualised and personality-focused prevention strategies, which are particularly needed to reverse the

increasing global burden of CVDs. Moreover, we found that care must be taken as spending more time outdoors may not be always beneficial specifically for cardiovascular health (Miguet et al., *Environmental Research*, 2021). We found a 20% increased risk for myocardial infarction incidence was observed among participants who reported spending more than 3.5 h/day outdoors compared to the reference group. A trend was also observed for stroke. These findings indicate that spending more than 3.5 h/day outdoors is a risk factor for myocardial infarction and stroke (Miguet et al., *Environmental Research*, 2021).

Decades of research have identified significant role of psychosocial factors specifically personality traits in the outcome and expression of cardiac illness but findings are inconsistent and the causal role of personality traits in the risk of CVD is not clear. Moreover, American Heart Association has identified well-being as one of the key factors to promote healthier lives for everyone in its 2030 goal. Yet, which measure of well-being should be prioritized is a matter of debate. Thus, by using powerful genetic instruments we investigated the causal association between well-being spectrum (comprised of four traits including neuroticism, depressive symptoms, positive affect and life satisfaction) and CVD, and found that higher well-being reduces the risk of CVD and among these studied well-being components, depressive symptoms is the key component (Rukh et al., 2022). Additionally, by further dissecting neuroticism into three genetically distinct sub clusters we tried to clarify the disputed association between neuroticism and CVD. We found that it is not worry or stress but actually it is the depressive component of this particular personality trait that causes increased risk for CVD (Rukh et al., *Frontiers in Genetics* 2022). These findings helps us to understand that depression that is very important risk factor for CVD and needs to be considering when assessing other risk factors such as stress or anxiety or higher levels of neuroticism. This may suggest that interventions aimed at reducing CVD should integrate strategies to promote psychological well-being specifically lowering down depressive symptoms.

Overall, the studies provide strong evidence of causal link between well being and risk for CVD. The studies highlight the importance of both looking at the life style including physical activity as well as other factors that are associated with well being, such as personality and psychiatric health to understand the interaction of the working life including job satisfaction to CVD. The studies also provide deeper understanding of the potential importance of spending time outdoor in the job situations in comparison with spending time indoor and the risk for CVD. The studies show the importance of good power and the access to diverse phenotypes for drawing important conclusions.

A more detailed description of the progress of each study under each of the three project axes is described below:

1. Identification of risk groups for CVD in specific occupations

Study I: Miguet M, Rukh G, Titova OE, Schiöth HB. Important Difference between Occupational Hazard Exposure among Shift Workers and Other Workers; Comparing Workplace before and after 1980. International journal of environmental research and public health. 2020;17(20).

The existing literature supports that shift work is associated with multiple indicators of poor health but frequently neglects the potential impact of occupational hazards. This study aimed at describing and comparing the exposure to different workplace hazards among shift and other workers before and after 1980. Exposure to different workplace hazards (noise, dust, pollutant and other physical stressors) were analyzed among 119,413 participants from the UK Biobank cohort, comparing shift and other workers, after stratifying the analyses by time (before or after 1980). Potential confounding variables (sex, age, ethnicity, education level, occupational category and neuroticism) were adjusted for in the log-binomial regression.

Our results highlighted that shift workers had higher Prevalence Ratio (PR) than other workers of being exposed to almost all identified hazards either before or after 1980. They were also more likely to be exposed to multiple hazards compared to other workers, both before 1980 (PR: 1.25; 95% CI: 1.21 – 1.30) and after 1980 (PR: 1.34; 95% CI: 1.30 – 1.38). The prevalence of all measured risk factors was higher after 1980 than before 1980 among shift workers, whereas work environment has been overall improved for other workers.

Our findings suggest that changes at the workplace have benefited other workers more than shift workers as they are still more exposed to all occupational hazards. This higher exposure to different occupational risk factors among shift workers compared with other workers could perhaps in part explain the higher prevalence of non-communicable diseases reported in this population. In this respect, the present study adds to the existing shift work literature and aims to call attention to occupational health exposure among this specific population. The study is recently published in the *International Journal of Environmental Research and Public Health* (Miguet M, Rukh G, Titova OE, Schiöth HB. “Important difference between occupational hazard exposure among shift workers and other workers; comparing workplace before and after 1980.” *Int J Environ Res Public Health*. 2020 Oct 15;17(20):7495. doi: 10.3390/ijerph17207495).

Study II: Shahid H, Rukh G, Miguet M, Lind L, Schiöth HB. Association between neuroticism and CVD by occupational category. Manuscript

Previous studies have shown that personality traits may interact with social environment to produce certain health outcomes. For example, the interaction of neuroticism with socioeconomic status has been studied and the results highlighted that higher level of neuroticism is associated with higher inflammatory levels in people with low socioeconomic status only. The present study was designed to further investigate the association between neuroticism and CVD by considering various occupational categories.

This study has been conducted in a large population-based cohort (the UK biobank) among 375,713 individuals from middle to older age group (mean age: 56.24 ± 8.06) followed up for 7 years. The neuroticism score was assessed by a 12-item questionnaire at baseline, while information related to MI and stroke events was 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. In fully adjusted model, a one standard deviation increase in neuroticism score was associated with 1.05-fold increased risk for MI. Yet, more work is needed in this study to optimize the statistical models and to conduct sensitivity analyses to confirm the findings (Shahid H, Rukh G, Miguet M, Lind L, Schiöth HB. “Association between neuroticism and CVD by occupational category.”).

2. Effect of work- and non-work-related stressors and lifestyle factors on the development of CVD

Study III: Laura C, Olivo G, Ahsan R, Rukh G, Lind L, Schiöth HB. Role of psychosocial factors in mediating the association between physical aspects of workplace environment and cardiovascular health. Manuscript

Several risk factors for CVD have been identified in epidemiological studies, which contributed to understanding of disease development and progression. Among thus, physical aspects of the workplace have a strong impact on CVD development. However, little validating of the identified risk factors in larger samples with more statistical power has been performed, especially in studies with longitudinal design. Furthermore, there is a lack of

investigation into the interplay between physical workplace hazards or detriments, and psychosocial hazards. Information regarding physical aspects of the workplace environment was obtained from the employment questionnaire and the information regarding psychosocial variables was obtained from the mental health questionnaire administered at the assessment centers. We conducted mediation analyses to investigate the direct and indirect impact of the psychosocial factors on the relationship between working environment and maximum workload. Maximum workload during a fitness test has emerged as a new and reliable measure of cardiovascular health, and is a useful tool in conjunction with other parameters such as blood pressure, heart rate and different respiratory tests as a predictor of mortality. We, therefore, aimed to investigate the association of psychosocial factors and workplace environment with maximum workload and the interactions between these factors to suggest a pathway for the impact workplace environment and psychosocial tendencies may have on cardiovascular health.

Working in a very noisy, very dusty or very hot workplace was associated with decrease in maximum workload but no association was observed for working in a very cold workplace. All the studied psychosocial factors, except job satisfaction, showed significant association with the maximum workload. Significant interactions were observed between happiness and satisfactory family relationship and maximum workload. However, we did not observe any mediatory effect of psychosocial factors on the relationship between physical workplace environment and studied cardiovascular outcome. A manuscript based on these results is being prepared and hopefully will be ready for publication very soon (Laura C, Olivo G, Ahsan R, Rukh G, Lind L, Schiöth HB. “Role of psychosocial factors in mediating the association between physical aspects of workplace environment and cardiovascular health”).

Study IV: Miguet M, Olivo G, Ciuculete DM, Elmståhl S, Lind L, Schiöth HB. Perceived stress is related to lower blood pressure in a Swedish cohort. Scandinavian journal of public health. 2021:14034948211030352.

Job strain has been previously associated with higher risk for CVD, yet, the role of job-unrelated stress was less documented, and there was no consensus over its effects on blood pressure. Within the EpiHealth cohort, in a sample of 9,441 employed Swedish individuals, we explored the associations of systolic and diastolic blood pressure with job stressors (measured with the Job Content Questionnaire), and general stress (measured by the Perceived Stress Scale). In this study, we also investigated the modulatory effect of lifestyle on the relationship between blood pressure and job and non-job related stressors. To this aim,

we performed separate linear regression, first at an uncorrected model, then further adjusted for relevant lifestyle- and health-related parameters (sex, age, civil status, education, alcohol intake, physical activity, sleep duration, BMI, depression, shift work, hours worked per week, smoking).

At the uncorrected model, the two component of job strain (job demand and decision latitude) as well as general stress, were negatively associated with systolic blood pressure. However, when correcting for lifestyle and health parameters, only general stress was associated to decreased systolic blood pressure. We did not detect an effect of job strain on blood pressure, supporting the hypothesis that lifestyle factors might partially mediate the association between job-related stressor and blood pressure.

The results of this study were reported in a manuscript which has now been published in *Scandinavian Journal of Public Health*, in which we discuss several explanations for this paradoxical relationship between high general stress perception and low blood pressure, in regards to previous literature findings (Miguet M, Olivo G, Ciuculete DM, Elmståhl S, Lind L, Schiöth HB. “Perceived stress is related to lower blood pressure in a Swedish cohort.” *Scand J Public Health*. 2021. doi: 10.1177/14034948211030352).

Study V: Miguet M, Venetis S, Rukh G, Lind L, Schiöth HB. Time spent outdoors and risk of myocardial infarction and stroke in middle and old aged adults: Results from the UK Biobank prospective cohort. Environmental research. 2021;199:111350.

Time spent outdoors has been related to cardiovascular health with conflicting results, conferring either beneficial or harmful effects. The objective of this study was to investigate the associations between time spent outdoors and myocardial infarction and stroke in a large population-based cohort. A total of 446,469 participants from UK Biobank were included in the study of which 431,146 participants were followed for 7 years. Time spent outdoors was self-reported and participants were stratified into quantiles (spending less than 1.5, 1.5 to 2.4, 2.5 to 3.5 and more than 3.5 hours per day outdoors). Myocardial infarction and stroke events were either collected from hospital records and death registries or were self-reported by the participants. Binary logistic regression was used for cross-sectional analysis and Cox proportional hazard regression for longitudinal analysis. In addition to age and sex, analyses were adjusted for potential demographic (TDI, ethnic background, current employment status), lifestyle (alcohol intake frequency, current tobacco use, sedentary time and moderate-

to-vigorous physical activity) and health related (BMI, systolic and diastolic blood pressure) factors.

Our results indicate that both, in the cross sectional and longitudinal analysis, spending more than 3.5 hours/day outdoors was associated with higher risk for myocardial infarction, even when adjusted for demographic, lifestyle and health parameters. Indeed, we found a 17% increased risk for myocardial infarction incidence among participants who reported spending more than 3.5 hours/day outdoors (HR: 1.17, 95% CI: 1.05-1.32) compared to the reference group. The findings of this study, in the light of the existing literature, are published in *Environmental Research* (Venetis S, Miguet M, Rukh G, Lind L, Schiöth HB. “Time spent outdoors is associated with increased incidence of myocardial infarction: UK Biobank cohort study”. *Environ Res.* 2021 Aug;199:111350. doi: 10.1016/j.envres.2021.111350. Epub 2021 May 19).

Study VI: Dahlén AD, Miguet M, Schiöth HB, Rukh G. The influence of personality on the risk of myocardial infarction in UK Biobank cohort. Scientific reports. 2022;12(1):6706.

Personality is a strong determinant for several health-related behaviours and has been linked to the development of cardiovascular diseases. However, the reports of personality's mediating role have been inconsistent with no data available from large population-based cohorts. The study aimed to create proxies for the Big Five personality traits to examine the longitudinal relationship between personality and myocardial infarction in the UK Biobank. The study sample comprised of 484,205 participants (55% female, 45% male, mean age 56.4 ±8.1 years) from UK Biobank cohort with a mean follow-up of 7 years. The personality proxies sociability, warmth, diligence, curiosity and nervousness were created using self-reported data on psychological factors, mental health and social support, to match the facets of the Big Five traits. Myocardial infarction outcome information was collected from hospital records, death registries or was self-reported. Logistic regression and Cox proportional hazard regression was used to estimate odds ratio (OR) and hazard ratios (HR), respectively with 95% confidence intervals (CI) adjusted for demographics (age, sex, socioeconomic status, ethnicity), health-related factors (BMI, diabetes, systolic and diastolic blood pressure) and lifestyle factors (alcohol intake, smoking, and moderate-to-vigorous physical activity).

Diligence was found to be significantly associated with lower prevalent myocardial infarction [OR: 0.87; (CI: 0.84-0.89)] and lower incident myocardial infarction [HR: 0.88; (CI: 0.85-0.92)]. Sociability was also protective against prevalent [OR: 0.89; (CI: 0.87-0.92)] and incident [HR: 0.90; (CI: 0.87-0.93)] myocardial infarction. Conversely, nervousness inferred a

higher risk for both prevalent [OR: 1.10; (CI: 1.08-1.12)] and incident [HR: 1.07; (CI: 1.04-1.09)] myocardial infarction during follow-up. Sex-stratified analyses revealed that nervousness increases the risk for incident myocardial infarction among women [HR: 1.13; (CI: 1.08-1.19)] compared to men [HR: 1.05; (CI: 1.02-1.08)].

Our results suggest that persons with higher levels of diligence and sociability mimicking predominantly conscientiousness and extraversion personalities respectively are less likely to experience myocardial infarction, while personalities predominantly characterized by nervousness poses higher risk for developing myocardial infarction specifically among women. The findings of this study are published in *Scientific Reports* (Dahlén AD, Miguet M, Schiöth HB, Rukh G. “The influence of personality on the risk of myocardial infarction in UK Biobank cohort.” *Scientific reports*. 2022;12(1):6706.)

Study VII: Ruijter MJT, Dahlén AD, Rukh G, Schiöth HB. Association of Diligence and Sociability with Stroke: A UK Biobank Study on Personality Proxies. *Frontiers in bioscience (Landmark edition)*. 2022;27(8):231.

Neurotic personality has shown to be associated with decreased quality of life after a cardiovascular event such as stroke. However, fewer studies have focused on the effect of psychological aspects of personality on stroke occurrence and the results are inconclusive. Moreover, the associations between personality and stroke have so far only been studied in relation to stroke mortality. Many stroke survivors suffer severe impairment of quality of life due to sequelae such as aphasia, hemiparesis, depression and anxiety. The current study aimed to assess the association between personality and risk of stroke, regardless of mortality, using the power of the large-scale UK Biobank cohort. Both cross-sectional and longitudinal associations were investigated using three different models adjusted for demographic, health-related, and lifestyle factors. Though the UKB does not include data on the Big Five personality traits, besides neuroticism, proxies for the Big Five personality traits were developed for 482,535 participants using self-reported data on psychological factors, mental health and social support.

Diligence [HR = 0.92; 95% CI = (0.88, 0.96)] and sociability [HR = 0.93; 95% CI = (0.89, 0.97)] were associated with a lower risk of stroke incidence after controlling for demographic, health and lifestyle factors. However, nervousness, curiosity and warmth were not significantly associated with a risk of stroke incidence. Findings from this study concluded that individuals with higher levels of diligence and sociability may be at a reduced risk of

developing stroke. With respect to the debated role of neuroticism in relation to cardiovascular disease, there was no evidence of an association between nervousness and risk of developing stroke. Results from this study may be used to identify individuals with an increased risk for developing stroke. This study has been published recently (Ruijter MJT, Dahlén AD, Rukh G, Schiöth HB. “Association of Diligence and Sociability with Stroke: A UK Biobank Study on Personality Proxies.” *Frontiers in bioscience (Landmark edition)*. 2022;27(8):231.).

3. Estimation of genetic influence on the association between working conditions and CVD

Study VIII: Rukh G, Dang J, Olivo G, Ciuculete DM, Rask-Andersen M, Schiöth HB. Personality, lifestyle and job satisfaction: causal association between neuroticism and job satisfaction using Mendelian randomisation in the UK biobank cohort. Translational psychiatry. 2020;10(1):11.

Job-related stress has been associated with poor health outcomes but little is known about the causal nature of these findings. Prior research has identified many potential antecedents of job satisfaction, including both individual factors such as personality traits and education level and lifestyle factors such as physical activity. However, it is difficult to establish the causal nature of these associations because all data came from observational studies that fail to establish causality due to issues such as reverse causation and confounding. In this study, we employed Mendelian randomization (MR) approach to investigate the causal effect of neuroticism, education, and physical activity on job satisfaction. Trait-specific genetic risk score (GRS) based on recent genome wide association studies were used as instrumental variables (IV) using the UK Biobank cohort (N=315,536). Both single variable and multivariable MR analyses were conducted to determine the effect of each trait on job satisfaction.

We observed a clear evidence of a causal association between neuroticism and job satisfaction. In single variable MR, one standard deviation (1 SD) higher genetically determined neuroticism score (4.07 units) was associated with -0.31 units lower job satisfaction (95% confidence interval (CI): -0.38 to -0.24 ; $P=9.5 \times 10^{-20}$). The causal associations remained significant after performing sensitivity analyses by excluding invalid genetic variants from GRSNeuroticism ($\beta(95\%CI)$: $-0.28(-0.35$ to $-0.21)$; $P=3.4 \times 10^{-15}$). Education (0.02; -0.08 to 0.12 ; 0.67) and physical activity (0.08; -0.34 to 0.50 ; 0.70) did not show any evidence for causal association with job satisfaction. When genetic instruments for

neuroticism, education and physical activity were included together, the association of neuroticism score with job satisfaction was reduced by only -0.01 units, suggesting an independent inverse causal association between neuroticism score ($P = 2.7 \times 10^{-17}$) and job satisfaction.

Our findings show an independent causal association between neuroticism score and job satisfaction. Physically active lifestyle may help to increase job satisfaction despite presence of high neuroticism scores. Our study highlights the importance of considering the confounding effect of negative personality traits for studies on job satisfaction. The findings from this study resulted in a manuscript which is published in *Translational Psychiatry* (Rukh G, Dang J, Olivo G, Ciuculete D, Rask-Andersen M, Schiöth HB. “Personality, lifestyle and job satisfaction: Causal association between neuroticism and job satisfaction using Mendelian randomisation in the UK biobank cohort.” *Transl Psychiatry*. 2020 Jan 21;10(1):11. doi: 10.1038/s41398-020-0691-3).

Study IX: Rukh G, Ahmad S, Lind L, Schiöth HB. Evidence of a causal link between the well-being spectrum and the risk of myocardial infarction: A Mendelian randomization study. Frontiers in genetics. 2022;13:842223.

Association between psychological factors and cardiovascular disease (CVD) is well established through observational epidemiological studies. Four psychological traits including life satisfaction, positive affect, neuroticism and depressive symptoms are highly correlated reflecting a common underlying biology and constitute the well-being spectrum (WBS). Here, we aimed to investigate whether the association between WBS and incident CVD is causal. By employing two sample Mendelian Randomization (MR) approach and using summary statistics data from already published genome wide association studies (GWAS) of European origin, we investigated the total and direct effect of WBS on incident CVD outcomes including atrial fibrillation (AF), heart failure (HF), myocardial infarction (MI) and ischemic stroke. In multivariable MR (MVMR) analyses genetic instruments for traditional CVD risk factors (type 2 diabetes, smoking, systolic blood pressure, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol) were also taken into consideration.

Our results highlighted that genetically predicted WBS was associated with 38% lower risk for heart failure (odds ratio (OR): 0.62; 95% confidence interval [CI]: 0.50-0.78; $P: 2.2 \times 10^{-5}$) and 40% reduced risk of myocardial infarction (OR: 0.60; 95% CI: 0.47-0.78; $P: 1.1 \times 10^{-4}$). Of the WBS constituent traits, only depressive symptoms showed a positive causal

association with heart failure and myocardial infarction. Neither WBS nor WBS constituent traits were associated with atrial fibrillation and ischemic stroke. In multivariable MR analyses, when genetic instruments for traditional CVD risk factors were also taken into consideration, the WBS was causally associated with a reduced risk for heart failure (OR: 0.72; 95% CI: 0.58-0.88; P: 0.001) and myocardial infarction (OR: 0.67; 95% CI: 0.52-0.86; P: 0.002).

The results of our study provides evidence that a higher WBS is causally associated with a decreased risk of developing CVD and, more specifically, myocardial infarction; moreover, the association is mainly driven by depressive symptoms. These results support current guidelines that suggest improving psychological wellbeing may help in reducing the burden of cardiovascular disease. These results have been published (Rukh G, Ahmad S, Lind L, Schiöth HB. “Evidence of a Causal Link Between the Well-Being Spectrum and the Risk of Myocardial Infarction: A Mendelian Randomization Study.” *Frontiers in genetics*. 2022;13:842223.).

Study X: Rukh G, de Ruijter M, Schiöth HB. Effect of worry, depression, and sensitivity to environmental stress owing to neurotic personality on risk of cardiovascular disease: A Mendelian randomization study. Journal of personality. 2022

There is a growing evidence that neuroticism is associated with cardiovascular disease (CVD) and results from prospective clinical and epidemiological studies indicate increased risk of coronary artery disease and mortality among people with higher neuroticism score. On the other hand there are studies that do not support the association between neuroticism and CVD mortality suggesting a further need to explore the associations between neuroticism and CVD. Neuroticism score is derived from twelve neurotic behavioral domains from the Eysenck Personality questionnaire, and range from zero to 12, with higher a score corresponding to a higher degree of neuroticism. However, recent GWAS have observed considerable genetic heterogeneity between these individual items. Hierarchical clustering analysis identified three genetically homogeneous item clusters namely depressed affect, worry and susceptibility to environmental stress and adversity (SESA). In order to gain biological understanding, neuroticism should be studied in genetically more homogeneous clusters. Thus, we aimed to understand the causal association between neuroticism clusters and CVD.

By using summary statistics from recent GWAS, we extracted genetic instruments for both neuroticism clusters and CVD traits (AF, HF, MI and stroke) and conducted bi-directional

Mendelian randomization analyses to gain a deeper understanding of the effect of neuroticism on CVD. In forward MR analyses with neuroticism subclusters as exposures and CVD traits as outcomes, no causal associations between worry or SESA cluster and any of the CVD traits were observed ($p > .05$ for all). However, a higher risk of having heart failure (odds ratio (95% confidence interval): 1.32(1.12 to 1.56); $p = .0011$) and myocardial infarction (1.47[1.18 to 1.83]; $p = 6.3 \times 10^{-4}$) associated with depressed affect cluster was observed. In reverse MR analyses with CVD traits as exposures and neuroticism subclusters as outcomes, no significant associations were observed ($p > .05$ for all).

The results of this study suggest that individuals with high neuroticism who are more susceptible to depressive symptoms are at higher risk for developing heart failure and myocardial infarction and should be more carefully evaluated for CVD risk in clinical settings. These individuals can potentially benefit from interventions aimed at reducing depressive symptoms to decrease CVD risk. There is no evidence to suggest that being sensitive to environmental stressors or being more worried can increase the risk for CVD. The results of this study have been published in the Journal of Personality (Rukh G, de Ruijter M, Schiöth HB. “Effect of worry, depression, and sensitivity to environmental stress owing to neurotic personality on risk of cardiovascular disease: A Mendelian randomization study.” Journal of personality. 2022.).

4. Genomförda insatser för att resultaten ska komma till praktisk användning

A summary of the results and main findings, as well as list of relevant publications has been sent to Swedish Work Environment Authority (Arbetsmiljöverket, Avdelningschef för Kommunikation, Eva Ferndahl) and the Agency for Assessment of Health Technology & Social Services (SBU; Elisabeth Gustafsson), Swedish Occupational Health Professional Organizations (Sveriges Företagshälsor, Marie Dahlgren). We have offered to explain in more detail the findings and provide support up on request. Overall the articles have been published in journals with high readership within the respective fields gaining number of downloads and citations.

5. Publikationer, presentationer och annan spridning inom projektets ram *Publications, presentations and other dissemination within the framework of the project*

Overall we have drafted ten papers based on the data acquired from the EpiHealth and UK biobank cohorts, of which eight are already published in well-known journals (*Environmental*

Research (IF:8.43), Translational Psychiatry (IF:5.18), Journal of Personality (IF: 5.11), Scientific Reports (IF: 4.99), Frontiers of Genetics (IF: 4.27), Frontiers in Bioscience-Landmark (IF 4.00), International Journal of Environmental Research and Public Health (IF:3.4) and Scandinavian Journal of Public Health (IF:3.06)), and remaining two are under different stages of preparation. Below is the list of all the ten studies, both published and unpublished:

Published studies

1. Rukh G, Dang J, Olivo G, Ciuculete DM, Rask-Andersen M, Schiöth HB. Personality, lifestyle and job satisfaction: causal association between neuroticism and job satisfaction using Mendelian randomisation in the UK biobank cohort. *Translational Psychiatry*. 2020;10(1):11.
2. Miguet M, Rukh G, Titova OE, Schiöth HB. Important Difference between Occupational Hazard Exposure among Shift Workers and Other Workers; Comparing Workplace before and after 1980. *International Journal of Environmental Research and Public Health*. 2020;17(20).
3. Miguet M, Olivo G, Ciuculete DM, Elmståhl S, Lind L, Schiöth HB. Perceived stress is related to lower blood pressure in a Swedish cohort. *Scandinavian Journal of Public Health*. 2021:14034948211030352.
4. Miguet M, Venetis S, Rukh G, Lind L, Schiöth HB. Time spent outdoors and risk of myocardial infarction and stroke in middle and old aged adults: Results from the UK Biobank prospective cohort. *Environmental Research*. 2021;199:111350.
5. Dahlén AD, Miguet M, Schiöth HB, Rukh G. The influence of personality on the risk of myocardial infarction in UK Biobank cohort. *Scientific Reports*. 2022;12(1):6706.
6. Ruijter MJT, Dahlén AD, Rukh G, Schiöth HB. Association of Diligence and Sociability with Stroke: A UK Biobank Study on Personality Proxies. *Frontiers in Bioscience (Landmark edition)*. 2022;27(8):231.

7. Rukh G, Ahmad S, Lind L, Schiöth HB. Evidence of a Causal Link Between the Well-Being Spectrum and the Risk of Myocardial Infarction: A Mendelian Randomization Study. *Frontiers in Genetics*. 2022;13:842223.

8. Rukh G, de Ruijter M, Schiöth HB. Effect of worry, depression, and sensitivity to environmental stress owing to neurotic personality on risk of cardiovascular disease: A Mendelian randomization study. *Journal of Personality*. 2022, In press.

Manuscripts

1. Covill L, Olivo G, Ahsan R, Rukh G, Lind L, **Schiöth HB**. Role of psychosocial factors in mediating the association between physical aspects of workplace environment and cardiovascular health. *Manuscript*.
2. Shahid H, Rukh G, Miguet M, Lind L, **Schiöth HB**. Association between neuroticism and CVD by occupational category. *Manuscript*.