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# Deciphering Adult Autism

## *Exploring Polygenic Risk, Brain Structure, Well-being, Migraine, and Mental Health Disorders*

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**Abstract**

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This research work comprises four studies investigating mental health disorders, with a particular focus on Autism Spectrum Disorder (ASD, hereafter referred to as autism). The research integrates epidemiological perspectives and genetic frameworks to explore connections with well-being, conditions such as migraine, and neuroanatomical brain structure changes in adulthood, utilizing data from the large European population cohort, UK Biobank, with over half a million participants.

*Paper I* examined the relationship between job satisfaction, job tenure, and 16 self-reported physician posed diagnosed mental health conditions. The findings show that Neurotic & Stress Disorders, Eating Disorders, and Other Mental Health Disorders are strongly associated with lower job satisfaction and shorter job tenure, highlighting the impact of mental health on workplace participation. Personality trait neuroticism significantly influences job satisfaction but not job tenure.

*Paper II* explored the relationship between genetic predispositions for autism and five well-being traits (neuroticism, depression, loneliness, life satisfaction, and positive affect). Polygenic risk scores (PRS) for autism were significantly associated with decreased well-being, particularly an increased risk of negative traits such as neuroticism and depression, and reduced positive traits such as life satisfaction, highlighting the genetic basis of well-being in individuals with autism.

*Paper III* examined the genetic link between autism and migraine, revealing that individuals with a genetic predisposition for autism have an increased risk of migraine, including both major types, migraine with and without aura. While no moderating effect of sex was found, personality trait neuroticism significantly mediated the relationship between autism and migraine, emphasizing the complex genetic and pathophysiological connections between autism and migraine, with neuroticism playing a key role in mediating this association.

*Paper IV* investigated the association between autism polygenic risk scores and brain volume alterations in the cerebellum, brainstem, and global brain structures in adults. The results demonstrated significant correlations, with higher autism PRS linked to reduced brain volumes, particularly in the cerebellum and brainstem, highlighting the genetic influence on neuroanatomical changes in autism adulthood.

These studies highlight the intricate connections between mental health, genetics, and brain structure, offering valuable insights for improving workplace participation and well-being in individuals with mental health issues including autism.

*Keywords:* Genetic risk score, mental health disorder, autism, migraine, well-being, MRI, brain

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*Dedicated*
*To my beloved wife* ***Saima!***
*This is the fruit of our doctoral journey!*

# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **Mohammad, S.**, Miguet, M., Rukh, G., Schiöth, H.B., Mwinyi, J. (2023) Job satisfaction and job tenure of people with mental health disorders: a UK Biobank cohort study. *Scandinavian Journal of Public Health*, 51(8):1248-1257

II. **Mohammad, S.**, de Ruijter, M. J. T., Rukh, G., Rask-Andersen, M., Mwinyi, J., Schiöth, H. B. (2023). Well-being spectrum traits are associated with polygenic scores for autism. *Autism Research*, 16(10): 1891–1902

III. **Mohammad, S.**, Bussu, G., Rukh, G., Schiöth, H.B., Mwinyi, J. (2024) Migraine and its major subtypes - with and without aura are associated with polygenic scores for autism. *(Manuscript submitted, under review)*

IV. **Mohammad, S.**, Gentreau, M., Dubol, M., Rukh, G., Mwinyi, J., Schiöth, H.B. (2024) Association of polygenic scores for autism with volumetric MRI phenotypes in cerebellum and brainstem in adults. *Molecular Autism 15*(1), 34

# Contents

# Abbreviations

| | |
|---|---|
| UKB | UK Biobank |
| PRS/PGS | Polygenic risk score/Polygenic score |
| ASD | Autism spectrum disorder |
| SNP | Single nucleotide polymorphism |
| GWAS | Genome-wide association studies |
| MRI | Magnetic resonance imaging |
| WBS | Well-being spectrum |
| CSF | Cerebrospinal fluid |
| GM | Gray matter |
| WM | White matter |

# Introduction

Mental health is a state of well-being that enable individuals to deal with life's challenges, realize their potentials, learn, work effectively, and contribute to their communities [1], encompassing both intrinsic and instrumental values, essential to overall well-being. **Mental health disorders** involve significant disturbances in cognition, emotional regulation, or behavior. In 2019, 1 in 8 people globally suffered from mental disorder [2], and in the U.S., 26% of adults experience a diagnosable mental disorder each year [3]. These disorders are prevalent in industrialized nations, affecting both individual well-being and societal integration. Economically, productivity losses due to these conditions far exceed the direct costs of care. In 2019, mental disorders accounted for 418 million disability-adjusted life years (DALYs) globally, representing 16% of global DALYs and an economic burden of approximately USD 5 trillion [4]. The link between mental health and job satisfaction is well-documented, with disorders like anxiety, depression, and emotional exhaustion contributing to job dissatisfaction and difficulties in maintaining employment [5–8]. Research often relied on limited number of self-reported mental health conditions at organization levels or physician-diagnosed conditions in small size clinical samples. There is a significant gap in large-scale studies at general population level, on job satisfaction and long-term workforce integration, addressing broader range of diagnosed mental health disorders.

Among wide range of mental health disorders, neurodevelopmental disorders are behavioral and cognitive conditions that arise during development, and involve difficulties in acquiring and performing intellectual, motor, language, or social functions, affecting around 15% of children and adolescents globally [9]. These disorders amongst others include intellectual development disorders, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD). **Autism spectrum disorder** (ASD; henceforth referred to as autism) comprises a group of complex neurodevelopmental disorders affecting about 1 in 100 children worldwide [10], with lifelong persistence and is marked by difficulties in social communication, restricted interests, and repetitive behaviors [11].

Decades of research have emphasized the importance of early detection and intervention to improve long-term outcomes for individuals with autism. Techniques like eye-tracking have identified early signs, such as reduced eye contact and attention disengagement, offering insights into the complexity of

the disorder [12]. The early development of predictive gaze in infants is particularly crucial for social cognition and interaction [13]. Machine learning method application for early identification of individuals with an elevated likelihood of autism, using minimal medical and background information [14]. Recommendations have also been made to enhance the learning environment for children with autism at the preschool level [15]. However, research on **adult autism** remains sparse, particularly beyond the transition into young adulthood, while the prevalence of autism in adults is comparable to that in younger populations [16]. Recent studies, such as one conducted in an adult outpatient psychiatric clinic in Sweden, have reported autism prevalence as high as 18.9% [17]. Little is known about life outcomes for adults with autism, especially in middle and older age, including well-being, personality development, comorbidities such as migraines, and changes in the mature brain, leaving gaps in knowledge and management strategies.

Emerging research suggests autism traits may exist on a continuum within the general population, challenging traditional binary diagnoses and highlighting the need for further research on autism's genetic and neuroanatomical connections [18]. Autism is highly genetic as evidenced by ~ 90% familial and twin based heritability [19, 20], and 11% single nucleotide polymorphism (SNP) based heritability [21]. Common genetic variants (minor allele frequency > 1%) contribute 11–49% to autism variance, in addition to strong associations with de novo protein-truncating variants (PTVs) and copy number variants (CNVs) [22, 23] in specific genes [21]. **Polygenic risk score** (PRS) method is a powerful tool that takes into account the cumulative totals of the SNPs that are susceptible for a specific trait or disease, with each SNP assigned a weight based on its effect size in association with the trait or disease, determined by genome-wide association studies (GWAS) [24].

PRS calculated from recent most and largest GWAS of autism currently explain a small proportion (2.5%) of autism variance [21]. However, PRS for autism have been successfully used as an index of this highly polygenic condition to investigate association with traits like childhood trauma, life-time self-harm, and suicidal behaviour and ideation [25], childhood difficulties in social communication [26], autistic traits [27], cognitive aptitude [28] and everyday executive function [29] in the general population. Alterations in brain structure, neuroanatomical changes such as cortical thickness [30, 31], surface area, gyrification [31], grey matter concentration [32] and neural density (preprint) [33] in relation to autism have also been successfully observed using autism PRS.

**Well-being** is a complex psychological construct [34] comprising traits like neuroticism, depressive symptoms, life satisfaction, and positive affect [35]. Adding loneliness to this framework improves the understanding " of the well-being spectrum (WBS) [36], with neuroticism, depression, and loneliness at the "negative-end" and life satisfaction and positive affect at the "positive-

end of the spectrum. Research indicates that individuals with autism often experience poor mental well-being [37] and lower quality of life [38–40]. Autism is associated with neuroticism [41–44] and mental health conditions like depression [45]. Those with autism also report increased loneliness [46–49], social anxiety [37], and lower levels of happiness [50, 51] and life satisfaction [52]. However, most research has focused on children and adolescents [53], and few genetic studies have examined well-being in relation to autism. Investigating this link genetically may enhance our understanding of well-being of the individuals with autism, and comprehensively with the application of WBS construct.

Individuals with autism frequently experience co-occurring conditions, with over 70% having additional medical, developmental, or psychiatric issues [54]. While many comorbidities, such as intellectual disability, ADHD, epilepsy, and anxiety, are well-studied, the link between autism and migraine, the most common neurological condition globally remains underexplored [55, 56]. **Migraine** is a primary headache disorder and a leading cause of disability affecting 15% of global population [57]. Autism and migraine exhibit similar pathophysiological changes, including neurotransmission dysregulation, especially within the serotonergic system; altered immune responses causing neurogenic neuroinflammation; cortical minicolumn organization abnormalities; and dysfunction in the gut-brain axis, along with shared susceptibility genes (comprehensive review[56]).

Previous research on the relationship between autism and migraines are limited, focused on children and adolescents. with small sample sizes, within clinical sample and with inconclusive results [58–60]. Some studies show a higher prevalence of migraines in children with autism, while findings in adults are inconsistent [61, 62]. Furthermore, while migraine is more common in women [63], autism is more prevalent in men [64], which highlights the need for research that explores the genetic and environmental factors that may explain sex-specific differences in this relation. Additionally, connections between autism and migraines with aura (group of neurologic symptoms like flashes of light, wavy linear patterns on the visual fields, or blurred vision), linked to sensory disturbances are rarely studied, despite shared characteristics such as early onset and cognitive impact [65–67]. A large population-based study among adults may assess the association between autism and migraine with high statistical power, reflecting on the under-explored population genetics of this association.

Decades of **magnetic resonance imaging** (MRI) studies on the brains of individuals with autism have provided structural and functional imaging insights that may aid in the diagnosis of the condition. The core symptoms of autism like social cognition and the role of the cerebellum have been well-established using MRI [68, 69], with autism-related genes co-expressed in the developing cerebellum and contributing to the pathogenesis of autism [70].

Cerebellar gray matter (GM) volumes have been linked to core autism symptoms [71], while disruptions in the brainstem are associated with various autism associated symptoms [72, 73]. Genetic factors influencing autism also drive structural and functional brain changes [74, 75], and neuroimaging genetics has emerged as a promising biomarker for early autism diagnosis [76].

However, MRI volumetric studies of autism have mainly focused on children and adolescents, revealing brain changes with age [77–79]. Common findings include accelerated brain growth in early childhood and deceleration in adolescence [80, 81]. In the past 15 years, few studies have explored cerebellar and brainstem volumetric changes in adults with autism. Recent case-control studies have produced inconsistent findings, with some reporting smaller brainstem and cerebellar volumes in autism, while others found no significant differences [82–84]. A meta-analysis by Yang et al. (2016)[85] reported reduced gray matter in the cerebellum of adults with autism, influenced by age, sex, and IQ. A longitudinal study by Lange et al. (2015) [86] showed atypical brain volume decline in autism from ages 6 to 35. While these studies have advanced the understanding of autism-related brain changes, most focus has been on children/adolescents and relied on case-control designs. The genetic link between autism and neuroanatomical changes among adults at general population level has remained underexplored.

The knowledge gaps featured here constitute the rationale and formulate the aims behind the research work discussed in this thesis.

# Aims

The overall goal of the papers included in the thesis was to investigate mental health disorders, particularly autism spectrum disorder (ASD) in an adult population, from various perspectives including epidemiological, genetic, and neuroanatomical aspects, focusing on daily living and disease concepts. Each paper pursued distinct research aim, summarized as follows:

- Paper I: To investigate and compare job satisfaction and job tenure among people with diagnosed mental health disorders in over 150 000 UKB participants. Additionally, explore the impact of socio-demographic characteristics, work-related factors and neurotic personality trait on job satisfaction and job tenure.
- Paper II: To investigate the genetic propensity for ASD using PRS, in association with the 5-WBS traits, which comprised (1) negative well-being traits including neuroticism, depression and loneliness, and (2) positive well-being traits, including life satisfaction and positive affect.
- Paper III: To investigate the association between genetic predisposition for ASD and diagnosed migraine, including its major subtypes, with and without aura, among adults in the UKB, using polygenic score analysis. Additionally, mediation and moderation analyses of the association between genetic risk for ASD and migraine.
- Paper IV: To investigate the association between ASD PRS and the volumetric MRI phenotypes in the cerebellum and brainstem among adults at the population level. Additionally, explore the whole-brain MRI volumetrics to investigate the global volumes of the brain, cerebrospinal fluid, gray matter, and white matter in relation to ASD PRS.

# Materials

## UK Biobank cohort

The projects listed in the thesis are based on data from the UK Biobank cohort (UKB). It is one of the largest prospective population-based cohorts in Europe of over 500 000 participants with deep genetic, phenotypic and imaging data. Details of each participant include data from questionnaires, physical measures, sample assays, accelerometry, multimodal imaging, genome-wide genotyping, and longitudinal follow-up for a wide range of health-related outcomes [87–89].

Participants aged between 40 and 69 years were assessed during 2006-2010 at 22 assessment centres throughout the UK. The assessment visit included electronic signed consent, a self-completed touch-screen questionnaire, a brief computer-assisted interview, physical and functional measures, and the collection of blood, urine, and saliva samples [89].The UKB genetic data contains genotypes for 488 377 participants. DNA was extracted from stored blood samples collected during participants' visits to a UKB assessment centre [88]. In 2014, UKB began the process of collecting imaging data by inviting participants, with a target of obtaining data for brain, heart, and body imaging for 100 000 participants [87].

Study samples of the studies included in the thesis, were considered taken in account the availability of data with intention to maximize the sample size. Exclusion criteria were set as per project relevance. In all projects, participants who '*withdrew their consent for participation'*, *'did not participate to relevant questionnaire'*, answered *'prefer not to answer'* or *'do not know'* or *'none of the given choice'* were excluded.

Additionally in *project I*, only properly employed participants were considered for final analysis. In *project IV*, participants were excluded if they had incomplete MRI data or reported a diagnosis of dementia, Parkinson's disease, multiple sclerosis, epilepsy, stroke, head or neurological injury, trauma, or other chronic neurological conditions (such as nervous system infections, brain abscess, encephalitis, demyelinating diseases, cerebral aneurysm, cerebral palsy, brain hemorrhage, or brain cancer).

Participant exclusion (in *project II, III, and IV*) related to quality control of polygenic risk score construction are mentioned in the 'Method section'.

## Ethical approval

Ethical approval for UKB data collection was granted by the North-West Multicentre Research Ethics Committee (11/NW/0382). Data usage in the thesis (under approved UKB application 30172) was further approved (2017/198) by the Regional Ethics Committee of Uppsala, Sweden.

## Funding

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# Methods

## Polygenic risk score analyses

PRS (or PGS) computation was conducted (*project II, III and IV*) for each UKB participant applying the 'clumping and thresholding' algorithms in PRSice-2 (version 2.3.5) [90, 91]. The latest iPSYCH-Psychiatric Genomics Consortium (PGC) autism GWAS summary statistics (November 2017) were used as the base dataset for PRS construction. The summary comprised 18 381 individuals with autism and 27 969 individuals from the general population of European ancestry [21]. Imputed genotyping data sourced from UKB were utilized as the target dataset for PRS construction.

Quality control (QC) procedures for PRS construction were followed according to recommended protocols using UKB data [88, 92]. The analyses were restricted to single nucleotide polymorphisms (SNPs) meeting specific criteria: a minor allele frequency (MAF) > 0.5%, an imputation information score (INFO) > 0.8, and genotype missingness < 2%. Participants meeting genetic data QC standards within the UKB were included, excluding individuals with missing rates > 2% on autosomes, displaying sex discrepancies, heterozygosity outliers, genetic relatedness up to third-degree relatives, or individuals not identified as 'White British' based on genetic grouping [92]. SNPs in linkage disequilibrium (LD) were clumped using an LD-based $r^2 \geq 0.1$ and a 250 kb genomic distance [93], and PRS for seven $P_{SNP}$ -value thresholds ($P_{SNP}$ = 1, 0.75, 0.5, 0.25, 0.1, 0.01, and 0.001) were generated [21].

In *Project II*, the *high resolution scoring* [91] method were applied additionally to produce 'best-fit PRS', that were identified as most predictive for each phenotype across the range P-value thresholds (pT = 0.0001 to pT = 0.5, in increments of 0.00005). ROC (receiver-operating-characteristic) curves (AUC) of the ASD PRS for each phenotype were used to evaluate predictive accuracy of the PRS models [92, 94, 95].

## Association analyses

Logistic and linear regression analyses were performed to investigate the associations between independent variables and dependent variables while adjusting for covariates as required per respective analyses. Regression coefficients beta ($\beta$) (in linear regression), odds ratio (OR) (in logistic regression)

and 95% confidence intervals (95% CI) were calculated. $R^2$ and Nagelkerke's pseudo $R^2$ (for binary phenotypes) represented the explained variance.

*P*-value significance (α) of < 0.05 was considered significant for the regression analyses and was corrected for multiple testing using Bonferroni method (*Project III*) and False-Discovery Rate (FDR) method [96] at 5% (*Project IV*). In *project II*, 'Empirical *P*-values' were obtained by permutation ($k$ =10,000) and considered as *P*-value significance (α) for each target phenotype [90, 97].

Statistical software IBM SPSS Statistics (version 26) and R (version 4.0.3) were used for analyses.

## *Ascertainment of the Variable*

*In Project I*, the dependent variables were 'job satisfaction' and 'job tenure', while sixteen mental health disorders were categorized into four groups and considered as the independent variables for analyses - (1) *Neurotic & Stress disorders (NSD):* Social anxiety/social phobia, Anxiety/nerves/generalized anxiety disorder, any other phobia (e.g. disabling fear of heights or spiders), Panic attacks, Agoraphobia and Obsessive compulsive disorder; *(2) Mood Disorders (MD):* Mania/hypomania/bipolar/manic-depression and Depression; *(3) Eating Disorders (ED):* Anorexia nervosa, Bulimia nervosa and Psychological over-eating/binge-eating; *(4) Other Mental Health Disorders (OMD):* Schizophrenia, Any other type of psychosis/psychotic illness, A personality disorder, Autism/Asperger's/autistic spectrum disorder and Attention deficit/attention deficit & hyperactivity disorder.

*In project II, III and IV*, the polygenic risk scores for autism (ASD PRS or ASD PGS) were considered as independent variables. The dependent variables for the analyses in *project II, III and IV* were five well-being spectrum traits (neuroticism, depression, loneliness, life satisfaction and positive affect), migraine and its major subtypes – with and without aura, and forty-four brain MRI phenotypes, respectively.

## *Ascertainment of the Covariates*

Covariates were considered in the projects to address any influence in the respective analyses. *In project I*, age, sex, educational status, townsend deprivation index (TDI), body mass index (BMI), physical activity, work hour and neuroticism were considered. Common covariates in PRS construction were age, sex, genotyping batch, and the first 15-20 genetic principal components (PC) for *project II, III and IV*. MRI imaging sites/scanners and, the x, y, and z coordinates of the head position in the scanner were additionally included as covariates in *project IV*.

## Mediation & Moderation analyses

Mediation and moderation analyses were performed (*Project III*) to investigate the effect of selected variables in the association analyses. A mediator was considered, if a variable served as a mechanism through which the independent variable influenced the dependent variable, acting as an intermediary variable. Conversely, a moderator was considered if a variable impacted the strength of the association between the independent and dependent variables, essentially functioning as an effect modifier (analogous to assessing an interaction effect).

Moderation effect of 'Sex' in the relationship was investigated (*Project III*). A series of mediation analyses were performed and seven potential variables (BMI, education, neuroticism, psychiatric comorbidities, vascular comorbidities, neurologic comorbidities, and other comorbidities) were considered for the mediation analysis. Bonferroni corrected 'α' was considered for mediation and moderation analyses. Package 'mediation' (version 4.5.0) in R using 1000 simulations was used to perform the mediation analyses.

# Results & Discussion

## Paper I

The *Paper I* aimed to investigate the association of job satisfaction and job tenure with self-reported physician posed diagnosed mental health disorders in a comprehensive European sample of population. While 16 mental health conditions, categorized into four groups (*Neurotic & Stress disorders*, NSD; *Mood Disorders*, MD; *Eating Disorders*, ED; *Other Mental Health Disorders*, OMD) taken in account, significant ($p$ <0.001) association were observed with lower job satisfaction and lower job tenure in all categories, independent of age, sex, TDI, BMI, education, physical activity, and working hours. However, personality trait neuroticism revealed a strong and independent impact specifically on job satisfaction, but not on job tenure.

Unlike earlier studies [5, 6, 98, 99] focusing on common disorders, a broader range of conditions were examined. While NSD ($\beta$ -0.22, 95% CI [-0.24, -0.19]) and MD ($\beta$ -0.23, 95% CI [-0.26, -0.21]) disorders linkage to lower job satisfaction were found and confirmed, strong association of ED ($\beta$ -0.24, 95% CI [-0.33, -0.16]) and OMD ($\beta$ -0.28, 95% CI [-0.40, -0.16]) with lower job satisfaction were found for the first time. Earlier research relied on self-reported conditions and smaller samples, focusing on overall physical and mental health, and the relationship to meaningful work [5, 6, 98, 99]. *Paper I* enabled the direct association of multiple mental health conditions with job satisfaction within one uniform large cohort, avoiding the high data heterogeneity often present in meta-analyses [100]. Additionally, using self-reported physician posed diagnoses helped to avoid the reporting bias that can arise from subjective and temporary evaluations of an individual's health state.

The inverse relationship of job tenure and mental health conditions confirmed the previous smaller-scale study observations (N ~ 60 to 326) ([8, 101–106] in general population, while adding wider range of investigated diagnoses . Specifically, it was observed that individuals with mental health conditions of all categories, NSD, MD, ED and OMD, tend to have shorter job tenures ($\beta$ -0.68, 95% CI [-1.04, -0.33]), ($\beta$ -1.00, 95% CI [-1.32, -0.68]), ($\beta$ -2.09, 95% CI [-3.22, -0.95]) and ($\beta$ -2.32, 95% CI [-3.89, -0.74]) respectively, compared to those without such conditions. Previous studies primarily focused on survival analysis predictions[101, 104, 105] or explored job termination within specific employment programs[7, 8, 102, 103, 106]. Moreover,

addressing job tenure across various mental health categories is limited in previous studies, predominantly concentrating on specific diagnosed conditions like general psychiatric disability [103, 105], schizophrenia, personality and mood disorders[7, 8, 101, 102, 104, 106].

A strong association between neuroticism and job satisfaction across various mental health conditions, consistent with previous research [107–110] was observed. A recent meta-analysis identified neuroticism as the strongest predictor of job satisfaction among the Big Five personality traits[111]. Additionally, a positive relationship exists between job satisfaction and the absence of negative affect [112]. Therefore, the high levels of neuroticism in individuals with mental health problems possibly make significant contribution to lower job satisfaction [111–113]. An exception with mood disorders (MD) were observed, showing strong association with job satisfaction independent of neurotic personality trait. This aligned with longitudinal and genetic study findings indicating that neuroticism reflects liability to depression [114]. Few studies with small sample size (*Fortin et al.*[115], N = 82), have investigated personality factors in employment and found that negative personality traits are linked to delays in job acquisition but not job retention or tenure. Our findings support this, showing that neuroticism does not affect job tenure, confirming previous results [115].

The study's **strengths** included high statistical power, extensive data on lifestyle and sociodemographic factors, and convergence of 16 mental health diagnoses, allowing for broadly applicable conclusions. However, certain **limitations** need to be acknowledged. *First*, the time difference between the collection of job related data and mental health data collection was a limitation in the cross-sectional analysis. *Second*, the category OMD contained a wide range of different mental health diagnoses. *Third*, additional confounders like job environment related factors [8] or factors related to subjective well-being [112] consideration might have contributed more to the study. *Lastly*, the study was based on cross sectional data, not allowing to infer causality.

# Paper II

The association between the genetic propensity for ASD with the five well-being spectrum (WBS) traits including neuroticism, depression, loneliness, life satisfaction, and positive affect was aimed to be investigated in *paper II*. The findings revealed that individuals with a higher genetic predisposition for ASD are more likely to experience poor well-being in life irrespective of age and sex, taken in account significant positive association with the negative WBS traits, neuroticism ($R^2_{max}$ = 0.04%, $P < 1x10^{-4}$), depression ($R^2_{max}$ = 0.06%, $P < 1x10^{-4}$), loneliness ($R^2_{max}$ = 0.04%, $P < 1x10^{-4}$), and significant negative association with the positive WBS traits, life satisfaction ($R^2_{max}$ = 0.08%, $P < 1x10^{-4}$), positive affect ($R^2_{max}$ = 0.10%, $P < 1x10^{-4}$).

Previous studies link ASD with several 5-WBS traits, showing that individuals with ASD often have neurotic personalities [41–44], higher depression rates [45], increased loneliness [46–49], lower life satisfaction [52], and reduced positive affect in life [50, 51]. However, these studies were limited in small sample size (N ~ 35 to 920), relied on questionnaires, and focused on adolescents and or clinical samples. *Paper II* further investigated these findings by examining the genetic propensity for ASD in a non-clinical cohort of ~350,000 adults.

The findings revealed that individuals with more risk alleles for ASD are more likely to experience loneliness and lower positive affect, reporting the first genetic associations between ASD and these traits using genome-wide data. While ASD is highly heritable [116], loneliness [117] and positive affect [118] have modest heritability, suggesting a genetic overlap. Additionally, higher polygenic load for ASD were linked to increased neuroticism, higher depression rates, and lower life satisfaction, supporting recent findings on the genetic overlap between ASD and these traits [21]. *Paper II* comprehensively explored the life satisfaction across multiple domains [119], providing robust insights into the connection between subjective well-being and ASD compared to previous studies [120].

While the findings showed, individuals genetically predisposed to ASD are inclined to experience poor well-being in life, these results should be interpreted with caution, taken in account the gene-environment interactions. Well-being largely depends on environmental factors, and genes influence brain development and information processing rather than directly shaping well-being experiences. Therefore, modification of environmental factors may alter the outcomes. Early diagnosis and a supportive environment may improve well-being in those genetically predisposed to ASD.

## Paper III

In *paper III*, the genetic propensity of ASD association with migraine and its major subtypes, with and without aura were investigated. The findings revealed adults genetically predisposed to ASD are significantly prone to experience migraine (OR = 1.04, 95% CI = [1.02, 1.05], $P < 2 \times 10^{-3}$, $R^2_{max}$ 0.030%). Moreover, individuals with a higher genetic predisposition for ASD were more likely to experience both migraine major subtypes, with aura (OR 1.05, 95% CI [1.02, 1.07], $P < 2 \times 10^{-3}$, $R^2_{max}$ 0.028%) and without aura (OR 1.05, 95% CI [1.02, 1.07], $P < 2 \times 10^{-3}$, $R^2_{max}$ 0.034%). Centile-based analyses of the cohort revealed a 12% increase in migraine, a 21% increase in migraine without aura, and a 14% increase in migraine with aura, corresponding to higher genetic propensity for ASD.

Only a handful of studies have reported a relationship between ASD and migraine, typically with small sample sizes and focusing on children or adolescents in clinical settings [58–60, 121]. Most studies reported a positive association between ASD and migraine [59–61, 121]. Population-based studies are scarce and show mixed results, with Lee et al. (2021) in Taiwan finding higher migraine likelihood in children with ASD [61], while Kaiser Permanente studies found lower or no significant prevalence in adolescents and adults [122, 123].

*Paper III* has been the first report of an association between ASD predisposition and migraine in adults, supporting previous findings of high neurological comorbidity [59] and increased autistic traits in migraine patients [124]. Shared pathophysiological and genetic elements, such as calcium channel mutations, neurotransmission dysregulation, and altered immune response, may explain this relationship [56, 125, 126].

Studies exploring association between ASD and migraine subtypes are very limited, with some reporting a positive link specifically between migraine with aura and ASD [60, 124] but however, limited by small sample sizes (N ~ 18 - 40) [60] and within only female cases with autistic traits [124]. *Paper III* demonstrated that both migraine subtypes are associated with a genetic risk pattern for ASD at a population level, supporting the link between migraine and ASD observed in smaller epidemiological studies [58–60, 121].

The effect of sex on the ASD-migraine association was investigated and found no moderating effect, which support the report by Sullivan et al. (2014) [58] of no gender differences in a small sample of children with ASD, and strengthens with robust observation at general adult population. Despite known sex differences in the prevalence of ASD (more in males) and migraine (more in females) [63, 64], the genetic link between ASD and migraine appears independent of sex. This finding contrasts with a Taiwanese study that found only male children with ASD had a higher migraine risk [61], while other studies reported a higher prevalence of migraine among females with ASD [122, 123].

Neuroticism was found to significantly mediate the association between genetic propensity for ASD and migraine, with a mediation effect of 8.75% (95% CI [0.04, 0.18]). Neuroticism is linked to difficulties in managing migraine pain [127], and influences vulnerability and coping strategies for pain [128]. This suggests that neuroticism may play a role in the ASD-migraine relationship by affecting pain perception [129].

## Paper IV

The *paper IV* aimed to investigate the association between ASD PRS and structural (volumetric) brain changes specifically in the cerebellum and brainstem, in addition to whole-brain MRI volumetric alterations among adults at

the population level. By investigating forty-four brain MRI phenotypes among ~ 31 000 individuals of European ancestry, ASD PRS were found significantly associated with the volumes of seven brain areas. The findings revealed that adults genetically predisposed to ASD exhibit a significantly reduced total brain volume, WM volume, and brainstem volume, alongside with an increased CSF volume. Specifically, individuals with higher ASD PRS show a reduced volume in the cerebellar lobules I-IV, IX, and X, as well as vermes VIIIb and X.

The results highlighted intriguing changes in the mature brains of adults at risk for ASD, contrasting with previous studies that predominantly focused on the developing brains of children and adolescents These earlier studies often reported increased brain volumes in younger participants with ASD [77–79]. The trajectory of volumetric changes with age in individuals with ASD has been widely discussed [78, 79], showing that early life in children with ASD involves accelerated brain growth leading to an enlarged brain. In contrast, typically developing children experience slight increases in brain volume, while individuals with ASD show a subsequent decrease [80, 130]. There is a consensus that ASD-related brain development involves increased growth of both GM and WM during early childhood, followed by a rapid synaptic pruning process during early adolescence [131, 132].

Adults with a higher genetic predisposition for ASD showed reduced total brain and WM volumes. This study has been the first to report a total brain volume reduction in adults at risk for ASD. Previous studies on WM volume in ASD showed mixed results, with some reporting increases and others decreases, particularly in cortical WM [79, 86].The findings aligned with previous studies showing a reduction in brain and WM volumes with age among individuals with ASD. Additionally, a significant correlation between reduced brainstem volume and elevated ASD PRS was observed, consistent with findings of brainstem structural abnormalities in ASD [72, 73]. Results also confirmed increased CSF volume in adults with ASD, consistent with previous findings [83, 133, 134]. The finding of increased CSF may be explained as CSF abnormalities is suggested to serve as an early biomarker for ASD, while neuro-inflammation and cognitive issues are linked to impaired CSF production, drainage, and recycling [135].

The investigation demonstrated that individuals genetically predisposed to ASD have reduced cerebellar volume in regions including the lobules I-IV, specifically in the left hemisphere, IX, and X, as well as the vermes VIIIb and X. This aligns with previous findings of decreased GM volume in the anterior lobe of the cerebellum (lobule I-V) and lobule IX in children with ASD [71]. These regions are linked to stereotypical behaviors and communication skills, suggesting cerebellar differences observed in children persist into adulthood. Additionally, reduced GM in cerebellar region X were found significantly associated with ASD PRS, supported by recent studies showing reduced volume

in this region correlating with ASD symptom severity [136], post-mortem reports of cell migration abnormalities[137] and lower Purkinje cell density [138]. These findings suggest cerebellar region X involvement in ASD symptoms.

Cerebellum volumetric analyses at the sub-regional level revealed that, adults with a genetic predisposition for ASD have reduced volumes in the left cerebellar region I-IV and vermes VIIIb and X. Few studies have examined adult ASD at this level, but overall cerebellar vermis volume reduction in ASD is well-documented [134]. The findings align with previous reports showing decreased GM in vermis VIIIb from early childhood with no change in effect with age [139]. Reduced cerebellar vermis volume correlates with ASD symptoms such as impaired development, cognition, language, motor skills, and behavior issues [140]. A negative association between ASD PRS and GM volume in the left I-IV cerebellar region was also observed. In children with ASD, reduced GM in the right I-IV cerebellar region correlates with greater severity in diagnostic interviews and social interaction scores [71]. This left-right asymmetry may be due to the altered lateralized neurodevelopment in ASD [141]. While ASD PRS were significantly associated with specific cerebellar regions, the total cerebellum volume was not affected, suggesting that genetic elements in ASD may specifically affect certain cerebellar regions rather than the entire cerebellum uniformly.

**Strengths** of these studies (paper *II, III, and IV*) included employing the powerful polygenic scoring tool, leveraging data from the latest and largest ASD GWAS (iPSYCH-PGC), alongside one of the most extensive cohorts with high-quality genetic and comprehensive epidemiological data (UKB). This approach ensured substantial statistical power and a reliable assessment of the phenotypes of interest. Furthermore, while large population-based cohorts often underreport ASD cases, they are enriched with high-quality genetic data, imaging data, comprehensive living-related outcomes, disease comorbidities, and detailed demographic information. The application of the PRS method in this context allowed for direct exploration of genetic data associated with underreported ASD diagnoses and facilitated the assessment of the phenotypes of interest. In *Paper II*, the novel combined approach, use of both the '*high resolution best-fit*' PRS and the '*empirical P value*' in PRS analysis is a strength as suggested to offer higher predictive accuracy compared to similar approaches [90, 91].

Nonetheless, these studies (paper *II, III and IV*) need to be also evaluated in light of their **limitations**. *First*, the UKB cohort is reported for a healthy volunteer bias [142], which may affect the generalizability of the findings. However, the study's focus on genetic propensity reduced potential confounding from other factors. *Second*, while the studies used the latest large GWAS data to construct ASD PRS, these scores explained only 2.5% of the variance in ASD, compared to a SNP-based heritability ($h^2_{SNP}$) of 11% [21]. Future research with larger GWAS and advanced PRS methods may improve the

findings. *Third*, the study focused only on common variants, not including the rare variants and copy number variations (CNVs), which account for < 5% of ASD liability [143–145]. Including these in future studies may refine the genetic assessments. *Finally*, these studies cannot establish causality due to the unidirectional nature of PRS predictions [146], though the findings contribute to strengthen and potentiate the epidemiological understanding evolving into correlations between ASD and various traits, while serving as a significant stride in potentially unravelling causality [147, 148].

# Conclusions

The findings across the studies in this thesis illustrate the significant relationships between mental health conditions, job satisfaction, genetic predispositions, and brain structure. The research highlights a strong connection between mental health issues and job dissatisfaction, as well as their impact on job tenure. Neuroticism was found to be strongly linked to job satisfaction but not to job tenure, highlighting its distinct role in workplace dynamics. Understanding these relationships and factors like personality traits is crucial for designing effective human resource strategies and services to improve workplace participation for individuals with mental health conditions.

The research also found that a genetic predisposition for autism is significantly associated with poorer well-being, offering new insights into the genetic mechanisms linking autism to well-being. Additionally, individuals genetically predisposed to autism are at an increased risk for migraines, including its subtypes with and without aura. This relationship is mediated by neuroticism, indicating shared genetic and pathophysiological mechanisms between autism and migraines that warrant further exploration.

The research also uniquely explores the associations between brain volumes, particularly in the cerebellum and brainstem, and polygenic risk scores for autism in adults. Significant correlations were found, suggesting that genetic susceptibility to autism may lead to structural brain changes, even in individuals who do not exhibit full symptoms of the disorder. Overall, the studies included in the thesis provide valuable insights into the complex interactions between genetic predispositions, brain structure, well-being, migraine, and mental health disorders, highlighting the need for further research and targeted interventions.

# Perspectives

**Translational research**, merging the research covering *Patient's bed to Researcher's bench*. Polygenic risk scoring (PRS) offers significant potential for advancing personalized management in autism and other mental health conditions. PRS can enhance early identification, personalized treatment, and behavioural therapy by evaluating genetic susceptibility to autism and comorbidities like anxiety, depression, and migraines.

Clinicians can use PRS to categorize patients by risk level, enabling personalized screening and early intervention strategies (*Risk Assessment and Prediction*). Such approach is already in practice for breast cancer in Netherland, and Sweden [149] will be the second country planning to integrate PRS for breast cancer in clinical practice.

In *precision medicine*, PRS may guide in development of management protocol for individuals with autism, by identifying subpopulations that may benefit from specific therapies. PRS can also provide valuable insights in genetic counselling, helping individuals understand their inherited risks and make informed decisions about family planning and lifestyle adjustments.

The *integration of PRS with other omics data* may improve our understanding of the shared genetic mechanisms underlying autism and its comorbidities. On a broader scale, large PRS studies can support public health initiatives by identifying high-risk populations, guiding preventive measures, and informing healthcare policy (*Public Health and Policy*).

While the future of PRS in clinical practice holds great potential for advancing personalized medicine, improving disease prevention, and refining healthcare interventions, it also requires thoughtful consideration of the ethical, legal, and social implications as its use becomes more widespread.

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