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Department of Surgical Sciences

Neuroscience Track

Investigating mental health disorders in relation to job and living related factors

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List of papers

1. **Mohammad S**, Miguet M, Rukh G, Schiöth HB, Mwinyi J. Job satisfaction and job tenure of people with mental health disorders: a UK Biobank cohort study. *Scandinavian Journal of Public Health*. 2022;0(0). doi:10.1177/14034948221119639

2. Well-being spectrum traits are associated with polygenic scores for autism, **Salahuddin Mohammad**, Markus J. T. de Ruijter, Gull Rukh, Mathias Rask-Andersen, Jessica Mwinyi and Helgi B. Schiöth (submitted to Journal: *Autism*)

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Abstract

Job satisfaction plays an important role for life quality and health of working individuals. While studies have shown that self-reported mental health conditions such as stress, anxiety and depression are associated with job satisfaction, a large population-based study exploring and comparing self-reported physician posed diagnosed conditions and their association with job satisfaction and job tenure is missing. First study addresses the gap along with exploring the impact of the neurotic personality trait and other possible contributing factors.

Individuals with autism spectrum disorder (ASD) experience lower well-being as demonstrated epidemiologically mostly for children and adolescents. Further etiological investigation of inclusive wellbeing, in terms of five wellbeing spectrum (5-WBS) traits including neuroticism, depression, loneliness, life satisfaction and positive affect, among adults with ASD may deepen the understanding. Seond study aims to investigate if a genetic predisposition for ASD is associated with 5-WBS traits using polygenic risk score (PRS) analysis.

In the first study, sixteen mental health disorders diagnosed by physicians, categorized into four major groups were investigated in relation to employment status (108,711 participants) and in relation to job satisfaction and job tenure (34,808 participants). Analyses were performed using linear regression adjusted for age, sex, TDI, BMI, education, physical activity, work hours and neuroticism. In the second study, PRS for ASD were constructed in the UK Biobank (N = 337,423), based on the GWAS conducted by Psychiatric Genetics Consortium (18,381 cases, 27,969 comparisons) using PRSice-2.

First study showed Neurotic & Stress Disorders, Eating Disorders and Other Mental Health Disorders were strongly associated with lower job satisfaction and shorter job tenure in both unadjusted and adjusted analyses. Neuroticism was strongly linked to job satisfaction but was not associated with job tenure. Second study showed, ASD PRS significantly predicted associations with all 5-WBS traits, showing a positive association with the negative WBS traits, neuroticism (max R2 = 0.04%, P < 1x10-4, AUC 0.51), depression (max R2 = 0.06%, P < 1x10-4, AUC 0.51), loneliness (max R2 = 0.04%, P < 1x10-4, AUC 0.51) and a negative association with the positive WBS traits, life satisfaction (max R2 = 0.08%, P < 1x10-4, AUC 0.56), positive affect (max R2 = 0.10%, P < 1x10-4, AUC 0.53).

Findings of first study clarify the complex relationship of mental health with job satisfaction and job tenure which is very important to understand in designing measures to improve working life participation of individuals with mental health issues. The findings of second study suggest that adults carrying a high load of susceptible SNPs for ASD are more likely to show a decreased well-being.

Background

Mental health is an integral part of well-being[1] and comprises cognitive, behavioural and emotional components. Any disorder of mental health affects the way we think, feel and act in our daily life[2]. A vital component of well-being is job satisfaction[3], which has been observed to be affected by mental health disorders[4]. Numerous studies have been conducted at an organizational level to study the mental health status of employees, detecting associations between job satisfaction and prevalent mental disorders like depression, anxiety or stress in specific occupations[4,5]. There is a broad range of mental health disorders which is underexplored in consideration to job satisfaction. Additionally, the vast majority of studies relies on self-reported diagnoses. Furthermore, a neurotic personality, has been shown to be related with job satisfaction[6]. Concerning the higher unemployment rate among individuals with mental health disorders[7], many studies addressed job acquisition and rehabilitation to integrate affected individuals in the job market[7–14]. Mental health disorders observed to be associated with a higher likelihood of early job termination[7]. However, investigations regarding job tenure focused mainly on employment programs for individuals with mental disorders. A limitation is, that these studies have always been limited in sample size and have focused on only severe psychiatric conditions[7–14]. While job satisfaction and job tenure are of great importance to be explored among individuals with mental health disorders[7], it is hard to find any population based study addressing the issues. Interestingly, no study has hitherto investigated job satisfaction in individuals based on expert diagnosed mental health disorders and covering broad range of conditions. Moreover, studies focusing job tenure have always been limited in sample size and in organizational level. A large population-based study may address these knowledge gaps, exploring and comparing diagnosed conditions in relation to job satisfaction and job tenure. Additional investigation can elucidate impact of the neurotic personality trait and other possible contributing factors.

A mental health disorder such as autism spectrum disorder (ASD) may be especially of interest in relation to well-being, due to its specific characteristics. ASD comprises a group of complex neurodevelopmental disorders with lifelong persistence and is characterized by challenges in everyday life, difficulties in social communication, restricted interests and repetitive behaviours[15]. ASD is highly heritable and affects almost 1-2% individuals in the population[16,17]. Interestingly, there is hardly any genetic study that has investigated well-being comprehensively in relation to autism. Well-being describes the individual optimal psychological functioning as a complex and broad construct composed of certain traits[18]. A separate line of research has identified genetic association of well-being spectrum, a spectrum consisting five well-being traits - 'neuroticism', 'depression', 'loneliness' at the "negative-end" cluster and 'life satisfaction', 'positive affect' at the "positive-end" cluster[18]. While previous studies have considerably advanced our understanding of the association between ASD and 5-WBS traits, these studies were primarily of epidemiological nature, focused on specific WBS traits separately, included only small cohorts, limited in clinical samples and most often children or adolescents [19–30]. There is a considerable gap of studies investigating well-being of ASD adults, whereas adulthood is the most stable period of age for such investigations [31]. Polygenic risk scores (PRS) based on susceptible single nucleotide peptides (SNPs) for autism have been shown to be associated with the likelihood for autism. Those PRS have been successfully used to investigate the association of autism with many different traits[32]. However, application of PRS to investigate association of well-being and ASD is still underexplored. A comprehensive investigation of the 5-WBS traits in general population of adult age, in connection to the genetic predisposition of ASD may fill in these knowledge gaps and thus, explore the currently missing etiological context.

Aim of Project I:

To investigate and compare job satisfaction and job tenure among people with diagnosed mental health disorders in more than 150,000 participants of UK Biobank. Additionally, to explore the impact of socio-demographic characteristics, work-related factors and neurotic personality trait on job satisfaction and job tenure.

Aim of Project II:

This study aimed to investigate if a genetic predisposition for autism spectrum disorder (ASD) is associated with five well-being spectrum (5-WBS) traits using polygenic risk score (PRS) analysis. Specifically, explore the genetic propensity for autism in association with the 5-WBS; which comprises 1) negative well-being traits including neuroticism, depression and loneliness, and 2) positive well-being traits, including life satisfaction and positive affect.

Project I

Materials and methods

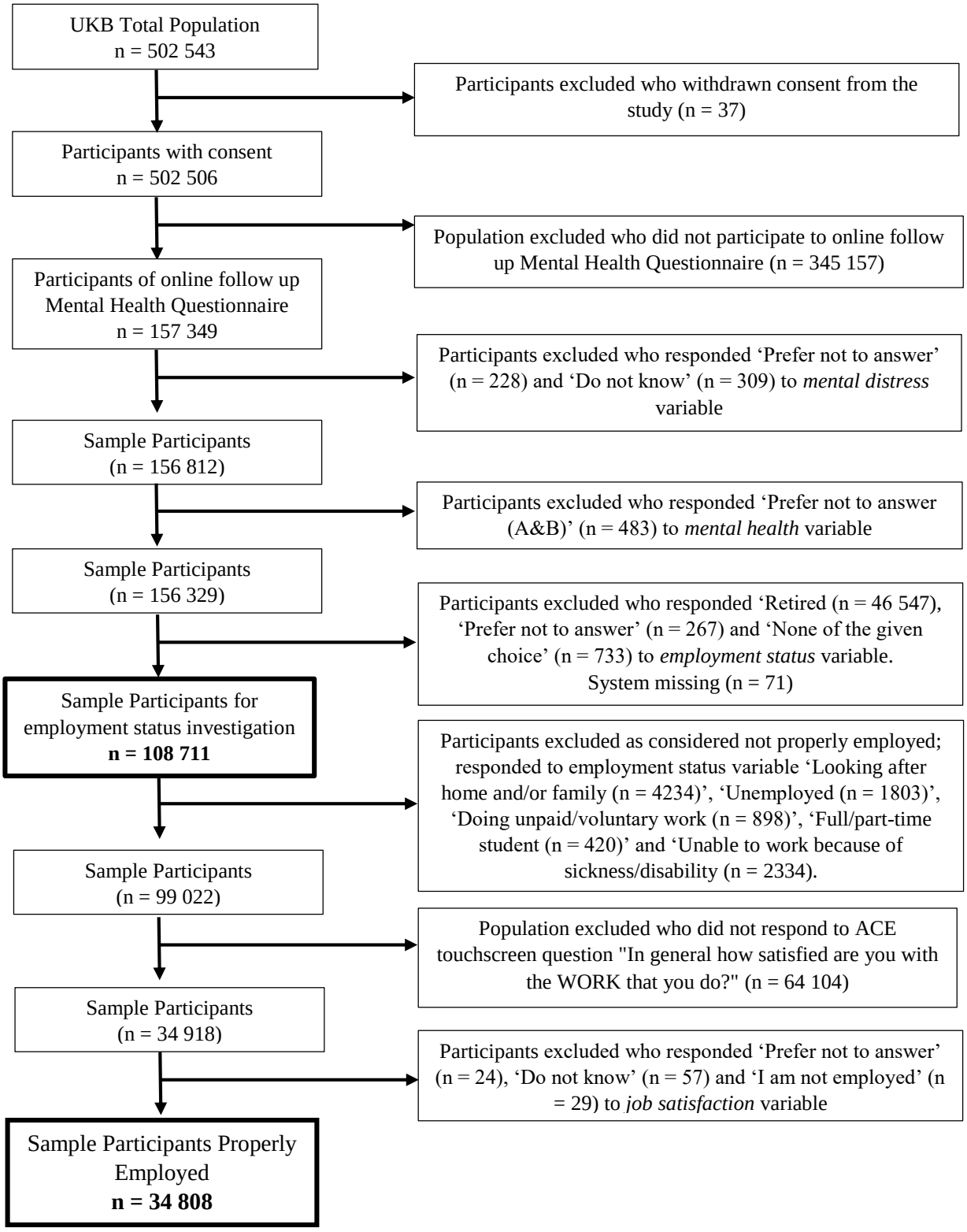
Study population: The UK Biobank

In this study data from the UK Biobank was used, which is an open source prospective cohort covering information for over half a million participants. The UK Biobank study collected a wide variety of data from general lifestyle phenotypes to genetic data. Ethical approval for UK Biobank study was granted from the NHS National Research Ethics Service North West (16/NW/0274) and the Regional Ethics Committee of Uppsala, Sweden further approved the data usage at our Department. Of the total UK Biobank population (N = 502,543), mental health disorders were investigated in relation to employment status (N = 108,711) and in relation to job satisfaction and job tenure (N = 34,808 participants) following exclusion and inclusion criteria in the study. Figure 1 shows the selection process of the participants included in the study.

Ascertainment of the variables and covariates

Information on job satisfaction was collected via the UK Biobank touchscreen question: "*In general how satisfied are you with the WORK that you do?*" and treated as an ordinal variable. A higher score corresponded to higher job satisfaction. Job tenure was defined as time (years) employed in the main job and explored with the question "*How many years have you worked in your current job?*". Higher values represented longer job tenure. We explored adults ever diagnosed with any mental health problem as self-reported, identified through the question "*Have you been diagnosed with one or more of the following mental health problems by a professional, even if you don't have it currently?*". Sixteen mental health disorders diagnosed by physicians and self-reported by the participant were categorized into four major groups for association analysis - (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. Except OMD, all other three categories were created according to ICD 10 protocol. The 'OMD' category was created to facilitate analysis and keeping in mind the widely acknowledged overlapping nature of mental health problems. As covariates, socio-demographic characteristics like sex, age, educational status, townsend deprivation index (TDI), body mass index, physical activity, personality trait neuroticism and occupation related variable like work hours were taken in account. Physical activity was extracted from the touchscreen-based questions by calculating the metabolic equivalent (MET) score, taking into account the weekly frequency and duration (in minutes) of walking, moderate physical activity and vigorous physical activity. Neuroticism was calculated as score based on the participants' response to 12 questions from the Eysenck Personality Inventory Neuroticism scale (EPIN-R). The score ranged from 0 to 12, where higher score represented higher level of neuroticism. Work hour was defined as the 'length (hours) of working week in job', where a higher value represented more working hours per week.

Figure 1: Flow chart of the cohort



Statistical analyses

Sample characteristics were summarized using frequencies, proportions and mean with standard deviation. We determined the regression coefficient (β) and 95% confidence intervals (95% CI) calculated by linear regressions to investigate the ordinal variable 'job satisfaction' and 'job tenure' distribution among the people with diagnosed mental health problems compared to relatively healthy people (reference) in the UK Biobank population. Both crude and covariate adjusted analyses were conducted. Adjusted analyses, to assess the influence of different covariates that might confound or mediate differences in the outcome, were conducted in two steps. In the first step, the analyses were adjusted for age, sex, TDI, BMI, education, physical activity and work hour. In the second and final step, analyses model was additionally adjusted for neuroticism to account for the influence of personality. A p value of < 0.05 was considered significant.

Results

We undertook initial analyses on 108,711 participants from UK Biobank who responded to the employment questionnaire (Figure 1). Table 1 shows the outcome of unadjusted analyses comparing individuals with and without mental health disorders. Higher unemployment rates were observed among people with mental health disorders in the four main categories investigated, i.e. Other Mental Health Disorders (OMD), 5% (n=52); Eating Disorders (ED), 2.2% (n=33); Mood Disorders (MD), 2.1% (n=519) and Neurotic & Stress disorders (NSD), 2.1% (n=410) compared to people without mental health disorders 1.5% (n=1,112). Among different mental health categories, individuals with OMD seemed to be mostly affected as compared to reference and other mental health categories, they showed highest percentage for the items 'Unable to work due to sickness/disability' 20.6% (n=215), 'Doing unpaid/ voluntary work' 1.5% (n=16) and 'Full/ part-time student' 0.8% (n=8) and are least represented in paid or self-employment. 67.4% (n=702). Moreover, individuals with ED showed the highest percentage in category 'Looking after home and/family' 6.8% (n=104).

TABLE 1. Employment status of UK Biobank population (Total, *N* = 108 711) who responded to Mental Health questionnaire

	Ref (*N*=72 988)	NSD (*N*=19 762)	MD (*N*=24 882)	ED (*N*=1 534)	OMD (*N*=1 042)
In paid employment/ self-employed	**67 618 (92.6)**	17 215 (87.1)	21 558 (86.6)	1 248 (81.4)	702 (67.4)
Looking after home and/family	**2 702 (3.7)**	858 (4.3)	1 090 (4.4)	104 (6.8)	49 (4.7)
Unable to work because of sickness/ disability	**729 (1)**	1 018 (5.2)	1 358 (5.5)	120 (7.8)	215 (20.6)
Unemployed	**1 112 (1.5)**	410 (2.1)	519 (2.1)	33 (2.2)	52 (5)
Doing unpaid/ voluntary work	**592 (0.8)**	175 (0.9)	219 (0.9)	18 (1.2)	16 (1.5)
Full/ part-time student	**235 (0.3)**	86 (0.4)	138 (0.6)	11 (0.7)	8 (0.8)

Values are expressed as *N* (%). NSD, Neurotic & Stress disorders; MD, Mood Disorders; ED, Eating Disorders; OMD, Other Mental Health Disorders.

Further analyses were undertaken on a sample of 34,808 individuals who were considered as properly employed according to the baseline assessment employment status questionnaire (Figure 1). Socio-demographic and occupational characteristics are summarized in Table 2. Mean age of the participants in the mental health disorders categories at the recruitment was comparable with the means age of reference group. Females were more likely to show mental health problems compared to males. Individuals in the ED group showed the highest gender dependent discrepancy. Individuals with reported diagnoses falling in the NSD and MD categories were found to be less educated and tend to be more obese compared to the reference group. Moreover, individuals with reported mental disorders were less deprived, were more likely to show signs of neuroticism, showed a similar physical activity profile and reported to work less hours per week compared to individuals without mental health problems.

Furthermore, individuals in different categories of mental health disorders were observed to be significantly (p <0.001) less satisfied with job and have significantly (p <0.001) shorter job tenure compared to the reference category. Individuals in the OMD group seemed to be least satisfied with their job, 4.1 (±1.1) and had shortest job tenure, 9.1 (±10.8) years compared to other mental health disorders and reference categories. (Table 2).

TABLE 2. Sociodemographic and Occupational profile of UKB participants (Total, N = 34 808) who reported to be properly employed

	Ref (*N*=23 806)	NSD (*N*=5 983)	MD (*N*=7 650)	ED (*N*=469)	OMD (*N*=236)
Age	**53.4± 7.2**	52.7± 6.9	52.3± 6.9	51.3 ± 6.4	51.5 ± 6.8
Sex					
Male	**11 701 (49.2)**	1 946 (32.5)	2 388 (31.2)	39 (8.3)	108 (45.8)
Female	**12 105 (50.8)**	4 037 (67.5)	5 262 (68.8)	430 (91.7)	128 (54.2)
Education					
College/university	**11 695 (50.3)**	2 695 (45)	3 598 (47)	262 (55.9)	134 (56.8)
Other	**11 841 (49.7)**	3 288 (55)	4 052 (53)	207 (44.1)	102 (43.2)
TDI	**-1.4 ± 2.7**	-1.2 ± 2.8	-1.1 ± 2.8	-0.7 ± 2.9	-0.3 ± 3.1
BMI	**26.6 ± 4.4**	26.9 ± 4.9	27.3 ± 5.2	26.5 ± 7.3	27.4 ± 5.1
Physical Activity (MET Score)	**2248.4 ± 2182.7**	2162.7 ± 2122.5	2155.5 ± 2177.0	2290.7 ± 2154.3	1976.0 ± 2227.9
Neuroticism	**3.2 ± 2.8**	5.9 ± 3.3	5.8 ± 3.3	6.1 ± 3.3	6.1 ± 3.5
Work Hours (Per Week)	**35.2 ± 13.1**	33.5 ± 12.4	33.5 ±12.5	33.7 ± 12.8	32.0 ± 11.8
Job Satisfaction	**4.4 ± 0.8**	4.2 ± 1.0	4.2 ± 1.0	4.2 ± 1.0	4.1 ± 1.1
Job Tenure (Years)	**12.9 ± 11.4**	11.7 ± 11.2	11.0 ± 11.0	9.6 ± 10.5	9.1 ± 10.8

Values are expressed as N (%) or Mean ± Standard Deviation. TDI, Townsend deprivation index; BMI, Body Mass Index; NSD, Neurotic & Stress disorders; MD, Mood Disorders; ED, Eating Disorders; OMD, Other Mental Health Disorders.

An in-depth analysis was performed studying the association between job satisfaction, job tenure and mental health problems in adjusted calculations as displayed in Table 3. Individuals with mental health disorders in all four categories showed significantly lower job satisfaction, an effect that was seen when correcting for multiple covariates including age, sex, TDI, BMI, education, physical activity and work hour (p <0.001). Compared to individuals with no mental health diagnosis, individuals in the OMD group showed the highest deduction of job satisfaction followed by subjects in the ED, MD and NSD groups, respectively. Finally, the analyses were additionally adjusted for neuroticism and it appeared to have a strong impact on the association between job satisfaction and different mental diseases as observed in Table 3. The association remained only significant for individuals with MD (β -0.04, 95% CI -0.071 to -0.014) after correcting for neuroticism.

TABLE 3. Regression analysis of Job Satisfaction and Job Tenure among individuals with mental health problems (NSD, n=5 983; MD, n=7 650; ED, n=469; OMD, n=236) and individuals without any mental health problems (Ref, n=23 806) in UK Biobank cohort who reported to be properly employed.

	NSD		MD		ED		OMD	
	β (95% CI)	R^2	β (95% CI)	R^2	β (95% CI)	R^2	β (95% CI)	R^2
Job Satisfaction								
Crude	-0.22*** (-0.24 to -0.19)	0.01	-0.24*** (-0.26 to -0.22)	0.01	-0.22*** (-0.30 to -0.15)	0.00	-0.36*** (-0.47 to -0.25)	0.00
Adjusted for multivariate †	-0.22*** (-0.24 to -0.19)	0.03	-0.23*** (-0.26 to -0.21)	0.03	-0.24*** (-0.33 to -0.16)	0.02	-0.28*** (-0.40 to -0.16)	0.02
Adjusted for multivariate † and neuroticism	-0.03 (-0.06 to 0.00)	0.92	-0.04** (-0.07 to -0.01)	0.99	-0.06 (-0.16 to 0.03)	0.82	-0.05 (-0.18 to 0.09)	0.81
Job Tenure								
Crude	-1.22*** (-1.54 to -0.89)	0.00	-1.86*** (-2.15 to -1.57)	0.00	-3.27*** (-4.32 to -2.23)	0.00	-3.83*** (-5.29 to -2.36)	0.00
Adjusted for multivariate †	-0.68*** (-1.04 to -0.33)	0.73	-1.00*** (-1.32 to -0.68)	0.74	-2.09*** (-3.22 to -0.95)	0.75	-2.32** (-3.89 to -0.74)	0.75
Adjusted for multivariate † and neuroticism	-0.66** (-1.07 to -0.25)	0.74	-1.19*** (-1.56 to -0.82)	0.75	-1.83** (-3.07 to -0.58)	0.76	-2.44** (-4.23 to -0.66)	0.76

†Multivariate: age, sex, Townsend deprivation index (TDI), Body Mass Index (BMI), education, physical activity and work hour; NSD, Neurotic & Stress disorders; MD, Mood Disorders; ED, Eating Disorders; OMD, Other Mental Health Disorders.
*p<0.05, **p<0.01, ***p<0.001

To investigate the relationship of job tenure with mental health disorders, we performed regression analyses (Table 3). Mental health problems were consistently and significantly associated with lower job tenure in all models throughout all categories of mental health disorders. The strong effect remained even after adding neuroticism to the adjusted model. Individuals in the OMD group showed the highest deduction of job tenure followed by individuals in the categories ED, MD and NSD respectively.

Discussion

To the best of our knowledge, this study is the largest cohort data analysis that investigated the association of job satisfaction and job tenure with self-reported physician posed diagnosed mental health disorders in a comprehensive European sample. We found that people with diagnosis of different types of mental health disorders as experienced during life time show poor job satisfaction and lower job tenure. Both relationships were found to be independent of age, sex, TDI, BMI, education, physical activity and working hours. Additional adjustments with the personality trait neuroticism revealed a strong and independent impact of neuroticism specifically on job satisfaction, which was not observed with job tenure.

Our results show that diagnosed mental health disorders experienced during lifetime are associated with lower job satisfaction. The findings are based on comparative investigations of job satisfaction between individuals with and without mental health illness, addressing 16 mental health conditions categorized in 4 major groups (NSD, MD, ED and OMD) in a large European sample. Our study covers a broad spectrum of mental health conditions, in contrast to earlier studies[4,5,33,34] which investigated only highly

prevalent disorders such as anxiety, depression and burn-out/stress. In addition to confirming associations of 8 illnesses falling in the categories NSD and MD with lower job satisfaction, we report for the first time that diagnoses belonging to the categories ED and OMD are also strongly associated with job satisfaction. Previous reports[4,5,33,34] are mostly based on self-reported conditions and studied mainly isolated outcomes in smaller samples such as overall physical and mental health [4,5,33], and relationship to meaningful work[34]. Our study allows the direct association of several mental health conditions with job satisfaction within one large cohort, thus, avoiding a potentially high heterogeneity of data that may be abundant in e.g. meta-analysis approaches, which may limit the explanatory power[35]. Moreover, use of self-reported physician posed diagnoses, helped us to avoid reporting bias arising from very subjective, temporary evaluations of the individual's health state.

We observed that individuals in the OMD group have the relatively strongest association with job satisfaction, which comprises diagnoses that may be linked to Intellectual Disability such as disorders belonging to the *Asperger's or autistic spectrum disorder* and *Attention deficit hyperactivity disorder*. However, earlier studies detected higher job satisfaction in individuals with Intellectual Disability [36]. The different outcome needs to be interpreted with caution, due to the heterogeneity of the subgroup in our study that also includes other diagnoses such as *Schizophrenia* and *Personality Disorder*, that are related with job dissatisfaction[37]. Moreover, individuals with Intellectual Disability are reported to have insufficient and improper concept of job satisfaction[38], as their perception of work could be related to the opportunity to stay social and this could be translated to overly positive characterisation of work.

We found that job tenure was inversely associated with mental health conditions. Here, we confirm previous small scale (N ~ 60 to 326)[7,9–14] studies, adding a wider range of investigated diagnoses. We observed that individuals with mental health conditions show shorter job tenure compared to healthy individuals. Earlier studies performed mainly survival analysis predictions[9,12,13] or studied job termination in different employment programs[7,10,11,14,37]. Literature on job tenure in relation to various mental health categories is scarce and has mostly focused on limited diagnosed conditions such as general psychiatric disability[11,13], schizophrenia, personality and mood disorders[7,9,10,12,14,37]. Thus, our study is unique regarding the broad spectrum of mental health diagnoses investigated.

The association between lower job tenure and mental health disorder was strongest among individuals in the OMD group, followed by individuals in the categories ED, MD and NSD. This outcome may be a result of the aspect that individuals with *Schizophrenia* or *Personality Disorders* were included in the OMD group [7,9,10,12,14,37]. As noted in our unadjusted analyses, individuals in the OMD category most often responded with 'Unable to work because of sickness/ disability' and fell most often in the lowest paid employment section compared to other categories, which may also explain the shortest job tenure of this group. These results have to be interpreted with caution due to the heterogeneity of the data in this group and the small sample size.

We show a strong association of neuroticism with job satisfaction throughout different mental health conditions in line with previous evidence[39–42]. A recent meta-analysis reported that the neurotic personality trait is the strongest predictor for job satisfaction among the big five personality traits[6]. Furthermore a positive relationship between job satisfaction and absence of negative affect in life has been shown[43]. Thus, the abundance of neuroticism in individuals with mental health problems is likely to be one of the main factors for lower job satisfaction in line with previous findings [6,43,44]. One exception from this is MD, for which strong associations between job satisfaction and mental disorders was found to be independent from the neuroticism score. This is in line with observations in longitudinal and genetic analyses showing that neuroticism strongly reflects the liability to depression[45]. Hitherto only a few studies with small sample size (*Fortin et al.*[46], N = 82) investigated personality factors with employment and found that negative personality traits were associated with a delay of job acquisition, but not with job retention or tenure. According to our results neuroticism does not influence job tenure, which confirms previous findings[46].

Interestingly, we observed that individuals with mental health disorders appeared to be less deprived and to work less hours per week. This may be explained by flexible work schedules and accommodation

like privileges as provided by employers to subjects with psychiatric disabilities[37]. The amount of physical activity was comparable in individuals with and without mental health conditions. Considering that physical activity may help in improving job satisfaction[44], we may assume that individuals with mental health disorders may benefit from being more physically active, however, further investigation in this domain is recommended to draw reliable conclusions. The strength of the present study is the high statistical power due to the large sample size of the UK biobank cohort. The availability of the detailed information covering lifestyle, sociodemographic factors and work-related parameters made it possible to correct for a considerable amount of potential confounding factors and allowed to draw conclusions for a general European population. Furthermore, the study includes large panel of mental health disorders covering 16 diagnoses, in contrast to most previous studies that include only 3-4 prevalent conditions. However, certain limitations need to be mentioned. First, the time difference between the collection of job related data and mental health data collection is a limitation in this cross-sectional analysis. It cannot be excluded that some of the individuals may have had some of the mental health related diagnoses in the 6 years after the baseline investigation. However, it can confidently be assumed that the vast majority of events have happened in the period up to baseline in the cohort of older individuals from 45 years upwards, as the covered diagnoses have their peak usually in younger years and the majority of collected person-years lies in the time frame up to the baseline investigation. It can be furthermore assumed that, mental health disorders tend to be chronic conditions which often lead to a long time history with delayed diagnosis as mentioned by us in the manuscript[47]. Second, the category OMD contained a wide range of different mental health diagnoses. We were not able to subcategorize individuals into groups of isolated diagnoses due to the strong overlapping nature of mental health disorders[48]. Third, we could have considered additional confounders in the analyses such as job environment related factors since job tenure relates to job environmental factors [7] or factors related to subjective well-being since they are as well associated with job satisfaction [43]. However, to keep our analysis as specific as possible and to avoid an overload of the models we decided to include factors most strongly related to job satisfaction. Lastly, the study is based on cross sectional data which does not allow to infer causality. However, we clearly observe that mental illness experienced during intellectual independently associates with job satisfaction and tenure. As thoroughly investigated in a recent meta-analysis [5], employees with mental health issues may suffer in their waking hours at work for long time, leading them to experience a lowering feeling of self-worth, feeling unfulfilled for long periods of working days or actual dissatisfaction. Moreover, job related components are different in each job facets and employees have different expectations from the organization when working in these facets[5,7]. These differences are important and may need to be addressed properly when considering the job satisfaction or job tenure of the employees. However, it can be hypothesized that a proper management of mental illness at the working place may notably improve the employment situation of affected individuals.

Project II

Materials and methods

Participants

Data from the UK Biobank (UKB) were used in the study. Details of UKB and ethical permission mentioned above. After standard quality control, 337 423 (*N*) participants (46% male) were considered for the study. Additionally, we identified 210 self-reported ASD cases (0.1%) in the UKB using data field 20544 ('Mental Health problems ever diagnosed by a professional').

Phenotypic information

The phenotypes of interest in the study were the 5-WBS traits (Histograms in supplementary Fig 1). Three phenotypes belonged to the negative end of the WBS, i.e. 'neuroticism', 'depression' and 'loneliness'. Two phenotypes belonged to the positive end of the WBS spectrum, i.e. 'life satisfaction' and 'positive affect'. UKB baseline data were used for the retrieval of the phenotypic information and

for the association analyses. The neuroticism score was measured on the included participants' (N = 274,266) response to 12 questions from the Eysenck Personality Inventory Neuroticism – Revised (EPIN-R) scale. The score ranges from 0 to 12, with higher scores representing a higher level of neuroticism. Information of depression were collected from included participants' (N = 335,328) response to the question *"Have you ever seen a general practitioner (GP) for nerves, anxiety, tension or depression?"*. Loneliness of included participants (N = 332,479) were assessed via the question *"Do you often feel lonely?"*. Information on life satisfaction of included participants (N = 74,607) were extracted from 5 touchscreen-based questions: 1) *"In general how satisfied are you with your family relationships?"*, 2) *"In general how satisfied are you with your financial situation?"*, 3) *"In general how satisfied are you with your friendship?"*, 4) *"In general how satisfied are you with your work?"* and 5) *"In general how satisfied are you with your health?"*. An average score was calculated for individual's life satisfaction, taken into account all five variables. A higher score corresponded to higher level of life satisfaction. Information on positive affect of included participants (N = 111,024) were collected based on the question *"In general how happy are you?"*, with higher score representing higher value.

Statistical analysis

Genotype quality control:

We used imputed genotyping data from the UKB and followed quality control (QC) steps as recommended for PRS construction while using UKB data. Analyses were restricted to SNPs with minor allele frequency (MAF) > 0.5, with an imputation information score (INFO) > 0.8 and genotype missingness < 0.02. We included only participants with quality controlled genetic data available in UKB to exclude individuals with a missing rate >0.02 on autosomes, with sex discordance, who were outliers for heterozygosity, who were genetically related (up to third-degree relatives) and of non 'White British' ethnicity based on genetic grouping.

PRS analyses and regression analysis:

PRS computation was done for each UKB participant using the clumping and thresholding algorithms in PRSice-2. The algorithm computes a polygenic score in a target sample by calculating the sum of all trait-associated alleles, weighted by the effect size of each allele in an independent sample generated from a base genome wide association study (GWAS). The latest iPSYCH-PGC autism GWAS summary statistics was used as the base dataset. This dataset was based on 18,381 autistic individuals and 27,969 individuals from the general population. The polygenic risk score calculated from the GWAS explained a variance of 2.45%, while using a unique Danish population based on five different sets of target and training samples. The SNP-based heritability (h^2_{SNP}) was calculated as 0.118.

Single neucleotide peptides (SNPs) in linkage disequilibrium (LD) were grouped together. We clumped SNPs using an LD based $r^2 \geq 0.1$ and a 250 kb genomic distance. PRS were calculated in *high resolution scoring* method to produce 'best-fit PRS', that is identified as most associated with the target trait, i.e. explaining a maximum variance (R^2) across the considered range of GWAS association P-value thresholds (pT). A range of pT = 0.0001 to pT = 0.5 at increments of 0.00005 was covered. Logistic and linear regression analyses were conducted to estimate associations between ASD PRS and phenotypes. Age, sex, genotyping batch and the first 20 genetic principal components were included as covariates in the model. 'Empirical *P*-values' were obtained by performing permutations *k* times (default = 10,000), where the target trait values were permuted across the individual values *k* times. The resulting empirical *P*-value was used to assess significance for each trait to control for Type-1 error and overfitting. The area under the ROC (receiver-operating-characteristic) curves (AUC) for the ASD PRS models of each trait were calculated to evaluate the predictive accuracy of the PRS model. PRSice 2.3.5 and R (version 3.6.3) were used for statistical analysis.

Results

Autistic individuals in the UK Biobank show increased rates for negative and lower rates for positive WBS traits

Prior to PRS analysis, we first investigated individuals with diagnosed ASD in relation to well-being. We observed that autistic individuals (N = 210, 'Methods') have increased mean scores for negative WBS traits and lower mean scores for positive WBS traits (Supplemental Table 1). Regression analyses investigating the association between WBS traits and ASD revealed positive associations with the negative WBS traits neuroticism (β 2.9, 95% CI 2.4 to 3.3, $P < 1x10^{-4}$), depression (OR 5.9, 95% CI 4.3 to 7.9, $P < 1x10^{-4}$) and loneliness (OR 4.45, 95% CI 3.4 to 5.9, $P < 1x10^{-4}$) and negative associations with positive the WBS traits life satisfaction (β -0.6, 95% CI -0.8 to -0.4, $P < 1x10^{-4}$) and positive affect (β -0.7, 95% CI -0.9 to -0.5, $P < 1x10^{-4}$) (Supplemental Table 1). Analyses were corrected for the effects of age and sex.

Autism PRS are associated with all three negative WBS traits

PRS for ASD significantly predicted all three negative WBS traits at all thresholds, as detailed illustrated in supplementary Figure 2. Figure 1 shows the results for the 'best fit' ASD PRS model for neuroticism (20 504 SNPs, $R^2 = 0.04\%$, pT = 0.07625, $P < 1x10^{-4}$, AUC 0.51), depression (60 844 SNPs, $R^2 = 0.06\%$, pT = 0.404, $P < 1x10^{-4}$, AUC 0.51) and loneliness (6 648 SNPs, $R^2 = 0.04\%$, pT = 0.01545, $P < 1x10^{-4}$, AUC 0.51). A detailed description of the high resolution best-fit PRS analyses of ASD for the negative WBS traits is given in Supplementary Table 2. Figure 2 shows the quantile plots for neuroticism, depression and loneliness, illustrating the positive associations between ASD PRS and all three negative WBS traits. Results demonstrate a stepwise increase of associations with increasing PRS loads (Figure 2).

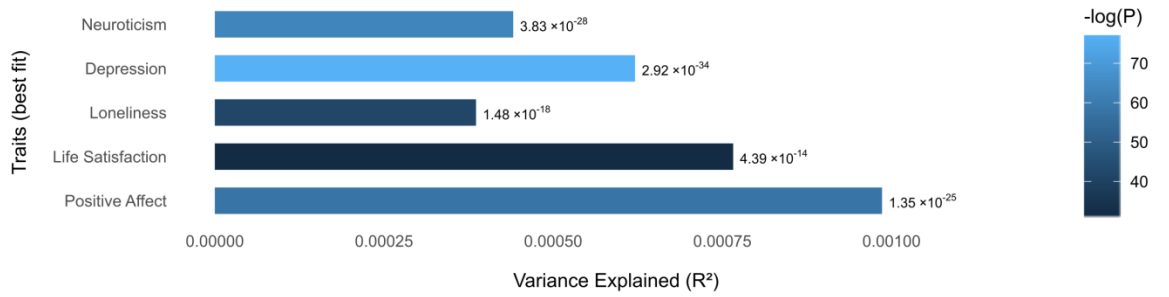


Figure 1 Associations between polygenic risk scores for ASD and the 5-WBS traits neuroticism, depression, loneliness, life satisfaction and positive affect. Values displayed next to each bar represent the *P*-value for significance for the most predictive (best-fit) models. The 'empirical *P*-value' significance threshold for all traits was set at $1x10^{-4}$ as found for every trait. Given that depression and loneliness were binary traits, the variance explained for these traits were measured using Nagelkerke's pseudo R^2.

Autism PRS are associated with both positive WBS traits

PRS for ASD significantly predicted both positive WBS traits, life satisfaction (853 SNPs, $R^2 = 0.08\%$, pT = 0.0009, $P < 1x10^{-4}$, AUC 0.56) and positive affect (50 192 SNPs, $R^2 = 0.10\%$, pT = 0.2924, $P < 1x10^{-4}$, AUC 0.53) as illustrated in Figure 1. Significant predictions were obtained at all thresholds as depicted in supplementary Figure 2. Details of the high resolution best-fit PRS analyses of ASD for the positive WBS traits can be found in Supplementary Table 2. Quantile plots for life satisfaction and positive affect show the inverse associations between ASD PRS and both positive WBS traits (Figure 2), demonstrating a stepwise decrease of these traits with increasing PRS loads.

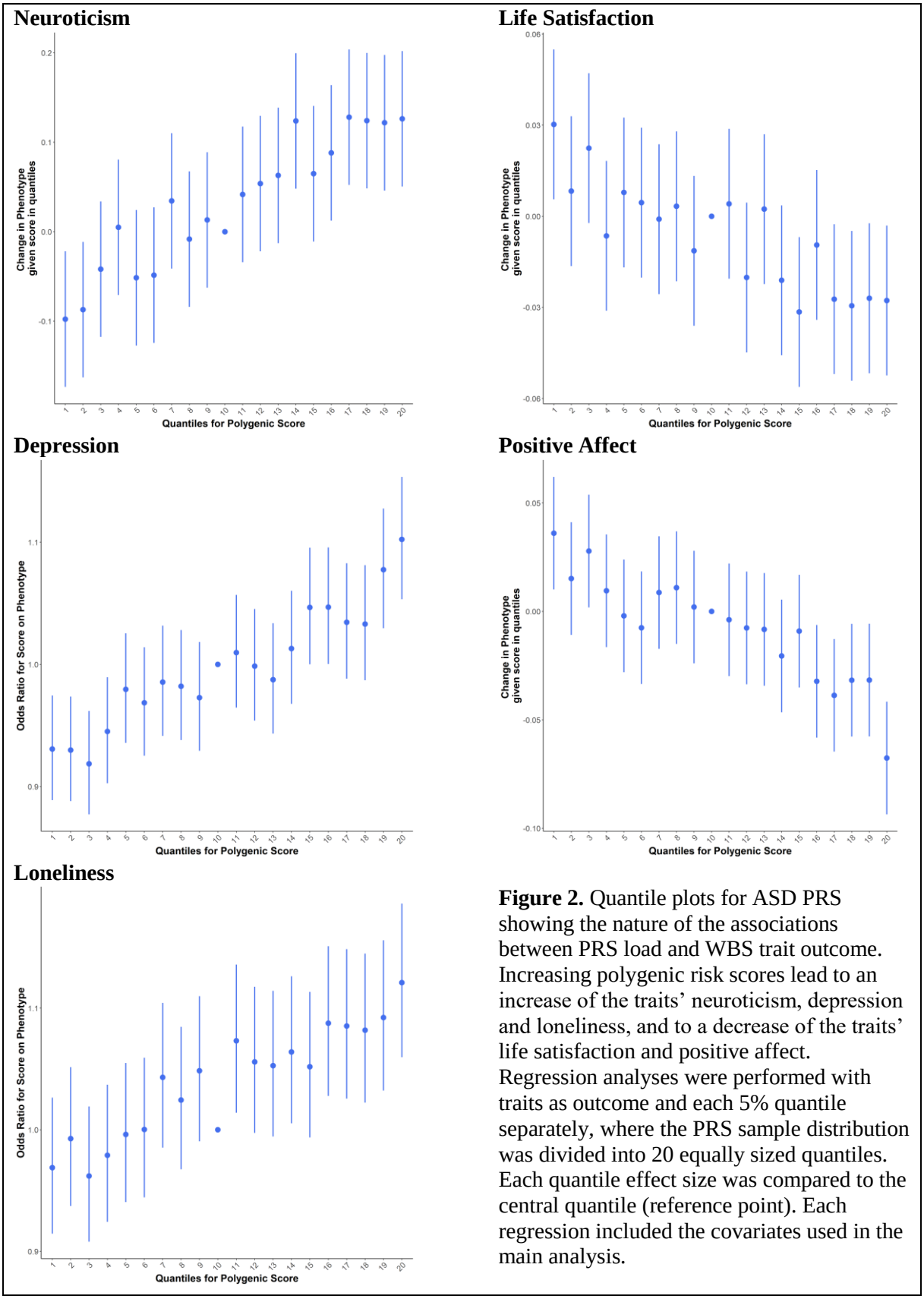


Figure 2. Quantile plots for ASD PRS showing the nature of the associations between PRS load and WBS trait outcome. Increasing polygenic risk scores lead to an increase of the traits' neuroticism, depression and loneliness, and to a decrease of the traits' life satisfaction and positive affect. Regression analyses were performed with traits as outcome and each 5% quantile separately, where the PRS sample distribution was divided into 20 equally sized quantiles. Each quantile effect size was compared to the central quantile (reference point). Each regression included the covariates used in the main analysis.

Discussion

This study is the first to investigate the genetic propensity of ASD to predict all the five well-being spectrum traits. We show that individuals with a higher genetic predisposition for ASD are more likely

to experience poor well-being in life irrespective of age and sex. Using PRS derived from the recently published largest GWAS for ASD, we detected that a higher polygenic risk for ASD is positively associated with the negative WBS traits 'neuroticism', 'depression', 'loneliness' and inversely associated with the positive WBS traits 'life satisfaction', 'positive affect'. Notably, this paper incorporates the first genetic evidence of associations between ASD and the well-being traits 'loneliness' and 'positive affect' giving further insight into the etiological nature of the association in connection to autism.

Our investigation on WBS demonstrates that individuals who are genetically predisposed to ASD show a significantly and overall reduced level of well-being. Previous epidemiological observations that investigated the 5-WBS traits in association with ASD, reported that individuals with ASD tend to show a neurotic personality [19–22], are more inclined to be depressed [23], have a higher likelihood to suffer from loneliness [24–27], and to experience lower life satisfaction [30] and lower positive affect in life [28,29]. However, besides one meta-analysis investigating the association between depression in ASD [23], all these epidemiological studies were hitherto characterized by sample size limitation, were questionnaire based and included mostly adolescents or clinical samples. Important examples include the observation that higher neuroticism associates with autistic traits as shown in (N ~ 37 to 828) clinical [19,20] and in (N ~ 201 to 320) population-based [21,22] studies. Furthermore, it has been shown that loneliness appears more often among adolescents with ASD (N ~ 35 to 85) [24–27] as well as poor life satisfaction (N = 46) [30]. A recent systematic review on Quality of Life [49] and small scale epidemiological studies (N ~ 52 to 120) [50,51] reported similar observations. Positive affect or happiness (used as interchangeable terms in different studies) was observed to be lower among individuals with ASD compared to non-ASD individuals in clinical samples of children (N ~ 408) [29] or in adults (N ~ 917) [28]. We provide genetic evidence and elaborate these findings by exploring genetic propensity for ASD using PRS in about 350,000 adults in a non-clinical cohort, strengthening the epidemiological observations by high statistical power and allowing to draw conclusions for a general adult population. It is important to highlight that our study is able to present results for all traits belonging to the 5-WBS based on the very same cohort, while earlier studies often focused on WBS traits separately.

We demonstrate that individuals with many risk alleles for ASD are more likely to show feelings of loneliness and a lower positive affect in life than those with fewer risk alleles. To the best of our knowledge, these are the first reports of genetic association of ASD with these traits based on genome-wide data. While ASD is known to be highly heritable [52], loneliness [53] and positive affect [54] have been reported as well to be of modest heritability. Therefore, it can be hypothesized that a genetic overlap of loneliness and positive affect with ASD may be abundant based on evidence of genetic predisposition association. However, to further strengthen the understanding, additional research is required to explore the genetic pathways and neurobiological mechanisms behind such associations.

Investigating the other three WBS traits neuroticism, depression and life satisfaction, we demonstrate that a higher polygenic load for ASD is significantly associated with higher rates of neuroticism, higher rates of depression and lower rates of life satisfaction. We observe that the nature of association is consistent with increasing polygenic load. Our analyses expand recent observations of the genetic overlap between ASD and these traits [16]. Furthermore, our study explored life satisfaction as an overall composite of the five domains of life, family relationship, financial situation satisfaction, friendship, work/job and health [55]. Thus, the analyses deliver robust results concerning the connection between subjective well-being [16] and ASD, taken the heterogeneity of 'subjective well-being' into consideration compared to earlier studies exploring with only a limited number of questions [56].

We show that the ASD PRS significantly predicted explained variance of WBS traits, where the variances explained were ≤0.10%. While these proportions may seem to be quite small, the magnitude is not unexpected to be found in a general population, as we investigate in our study. The observed percentages are roughly in line with previous studies investigating ASD PRS in association with other traits. Earlier studies observed rates of <0.5% for cognitive aptitude [57], 0.10%, 0.11% and 0.13% for 'childhood trauma', 'self-harm ideation' and 'self-harm' respectively [32]; 0.17% for 'childhood behavior', 0.24% for 'rigidity' and 0.54% for 'attention to detail' [58] and 0.41% for everyday executive

function [59]. Our presented quantile analysis further demonstrates the nature of the associations between PRS for ASD and traits of interest, and highlights the potential to stratify individuals at risk for ASD for their risk to show a decreased well-being based on their ASD associated PRS [60]. These observations highlight the robustness and strength of the findings. While our PRS is based on the latest available largest autism GWAS, the percentage of 'explaining variance' may be further increased by an even larger sample size of the discovery dataset and an enrichment of significant markers included in the GWAS [61]. We found the predictive accuracy of the ASD PRS to be in the range between 0.51 and 0.56 for the investigated 5-WBS traits, which is borderline accurate to establish prediction, considering 0.50 as the cut-off point for lack of discrimination [62]. However, the accuracy may further increase in power with a modest increase in the sample size of subjects in the discovery dataset or GWAS summary dataset [61]. In light of these aspects the findings made in our study can be considered robust.

While we show that individuals genetically predisposed to ASD are inclined to experience poor well-being in life, the results need to be interpreted with caution taken into account the gene environment interaction. Well-being largely depends on environmental factors, and genes instead of directly shaping well-being experiences, contribute in brain development and the processing of information acquired from the environment. Taking this into account, we hypothesize few prospective mechanisms by which genetic predisposition for ASD may be associated with well-being. First, elevated PRS for ASD could result in communication, social relationship and behaviour problems [58,63], which possibly in turn result in difficulties to cope at everyday places of life such as at home, at workplace and at friends' or relatives' places. This may lead to increased social distance or exclusion, and subsequently increase feelings of loneliness and lower life satisfaction [55]. Second, often receiving negative attitude from others since an early age, failing to achieve and being compared to others at different stages of life since birth may contribute to develop a neurotic personality and lower positive affect in life. Third, the lack of understanding of the own state of health, the late or absence of diagnosis of ASD (leading to lack of social support), as well as the difficulties with workplace and surrounding environments may explain the higher risk for depression among ASD individuals. Therefore, modification of environmental factors may alter the outcome considerably. For instance, early diagnosis and ensuring a supportive environment to genetically predisposed ASD individuals may improve well-being throughout adulthood.

Strengths of this study include the use of the powerful PRS tool that utilises the latest largest autism GWAS (iPSYCH-PGC) and one of the largest cohorts with quality genetic data (UKB), which allowed performing this study with high statistical power and a reliable assessment of 5-WBS traits reflecting comprehensive autism well-being. Our application of both, the '*high resolution best-fit*' *PRS* and the '*empirical P value*' combined approach in PRS analysis is first to report and have been suggested to have higher predictive accuracy than similar methods [64,65]. Application of the PRS method allowed the exploration of large cohorts that have high quality genetic data, but underreported ASD diagnoses such as UKB [323219201212](Warrier & Baron-Cohen, 2021). The applied PRS approach made it possible to directly assess the relationship of ASD with living related outcomes, which are often difficult to investigate in cohorts existing on autism [32].

There are a couple of limitations in this study to be mentioned. First, the UKB cohort is known to have a healthy volunteer bias [66] and we also observed lower ASD prevalence (0.1%) compared to the prevalence of ASD in the UK (1-2%) [16,17]; suggesting that the observed association of WBS traits with ASD may differ in the general population. However, the report [66] compares especially the demographic characteristics in UKB, while our study addresses the genetic propensity, which is fixed at birth and the reverse associations to be confounded by other factors are less likely. Second, while the PRS for ASD were constructed using the most recent and largest GWAS to date, it still explains only a lower total variance of 2.5% compared to h^2_{SNP} of 11% , which has been earlier described [16]. Third, although rare variants and CNVs contribute to a fractional variance in ASD [67], this study focused only on common variants. However, advancements in future GWAS with larger sample size and the application of advanced PRS methods as presented here may potentiate the understanding of the etiological associations observed in this study. Finally, our study cannot robustly infer causality, due to the fact that PRS predictions are only able to investigate a causal status in one direction [68]. Therefore, our

investigation strengthens and potentiates the epidemiological understanding of simple associations into correlations [69] between ASD and WBS, while acting as a potential step toward identifying causality [70].

Conclusions

Our project I study demonstrates a strong link between mental health conditions, job dissatisfaction and job tenure. Neuroticism was strongly linked to job satisfaction but was not associated with job tenure suggesting a differential role of this personality trait. Overall, our findings further shed light on the complex relationship of mental health with job satisfaction and job tenure. Detailed understanding these relationships and the possible relevant interacting factors such as personality traits are important to design measures like human resource trainings and services to improve working life participation of individuals with mental health issues.

The project II study shows that genetic predisposition for autism is significantly associated with poor well-being. The findings give new potential insights into etiological mechanisms underlying the connection of autism and poor well-being. Extending our findings in the future studies with direct assessments of ASD traits in individuals, using diagnostic tools like well-established questionnaire such as the Autism Spectrum Quotient (AQ) is recommended. Future advancement and empowering of autism GWAS with additional significant loci and a higher number of cases may enable the performance of Mendelian Randomization analysis for firmer causality assessments. Our study results support the importance to further optimize policies regarding supportive care for an improvement of well-being of individuals with ASD.

Next phases - Research plan

Autism and migraine association analysis – polygenic risk scoring approach

Autism spectrum disorder (ASD) is a group of complex neurodevelopmental disorders with lifelong persistence, and is characterized by challenges in everyday life, difficulties in social communication, restricted interests and repetitive behaviours [15]. Individuals with autism present with a broad range of co-morbidities or co-existing conditions compared to the general population including migraine [71]. Migraine is one of the most prevalent disorders worldwide [72]. Studying the association between autism and migraine is of great interest as both conditions share certain common genetic variants and pathophysiological pathways [73]. Surprisingly only a handful of studies have explored the association between autism and migraine [74–76] . Major limitations of these studies are the small sample size of ASD individuals (N = 18 - 105) [74–76]. A large population-based study may asses the association between autism and migraine with more statistical power. Furthermore, earlier comorbidity studies focused mostly on the epidemiological context and the common genetic susceptibility of autism and migraine has only been partly explored[77].

In our previous project we used UK Biobank data and successfully applied the polygenic risk scoring method to investigate the association between autism and well-being spectrum traits. UK Biobank is a prospective cohort of more than 500 000 participants' wide variety of data from general lifestyle phenotypes, medical history to genetic data [78]. Polygenic risk scoring allows taking into account all the susceptible genetic mutations cumulatively to predict the specific trait on target population and to perform the analyses on a large samples size. A similar approach is also appropriate for the exploration of autism and migraine association.

Our aim is therefore, to investigate if a genetic predisposition for autism spectrum disorder is associated with diagnosed migraine cases in UK Biobank using polygenic risk score analysis.

Association analysis of adult brain MRI changes and polygenic risk scores for autism

Autism spectrum disorder (ASD) affects approximately 2% of the general population [79]. Reliable detection of ASD can provide the opportunity to offer support and thus lower the burden of the condition in daily life among affected individuals. Magnetic resonance (MR) examination is a powerful tool to investigate changes in the brain of individuals with ASD [80]. Recently, Rafiee et al. reviewed previous findings and recent advances on magnetic resonance imaging (MRI) analysis in ASD, and summarized the structural and functional changes that can lead to earlier detection of ASD[81]. However, the reviewed studies mostly focused on changes during childhood and adolescent, whereas the MRI changes in ASD adults are little explored. There are few studies that have explored brain changes as seen in adults with ASD. These studies focused on brain anatomy in relation to ASD behavioral symptoms (N = 89)[82], investigated certain brain regions across frequently co-occurring neurodevelopmental disorders including ASD (N = 489)[83] or investigated the frontal network (N = 61)[84]. Overall, these studies were limited in sample size (N = 61 – 489) and only included males. A wide population based study on MRI findings with higher statistical power, including both male and female subjects may provide elaborative knowledge on brain changes among ASD adults.

UK Biobank imaging data collection started on 2014 with the aim to include 100,000 subjects[78], and till now has around 39 690 participants with complete MRI scans. Experts have estimated that for every three diagnoses of ASD cases, two additional cases remain undiagnosed for ASD[85]. While this significant amount of undiagnosed probable ASD cases move on to adulthood, application of polygenic risk scoring of autism to explore adult autism related brain changes in the cohort like UK Biobank with extensive data may fill the knowledge gap.

Therefore, we aim to investigate autism associated changes in the adult brain and compare gender associated differences stratifying in accordance to the ASD polygenic risk score load observed in the individuals.

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Appendix

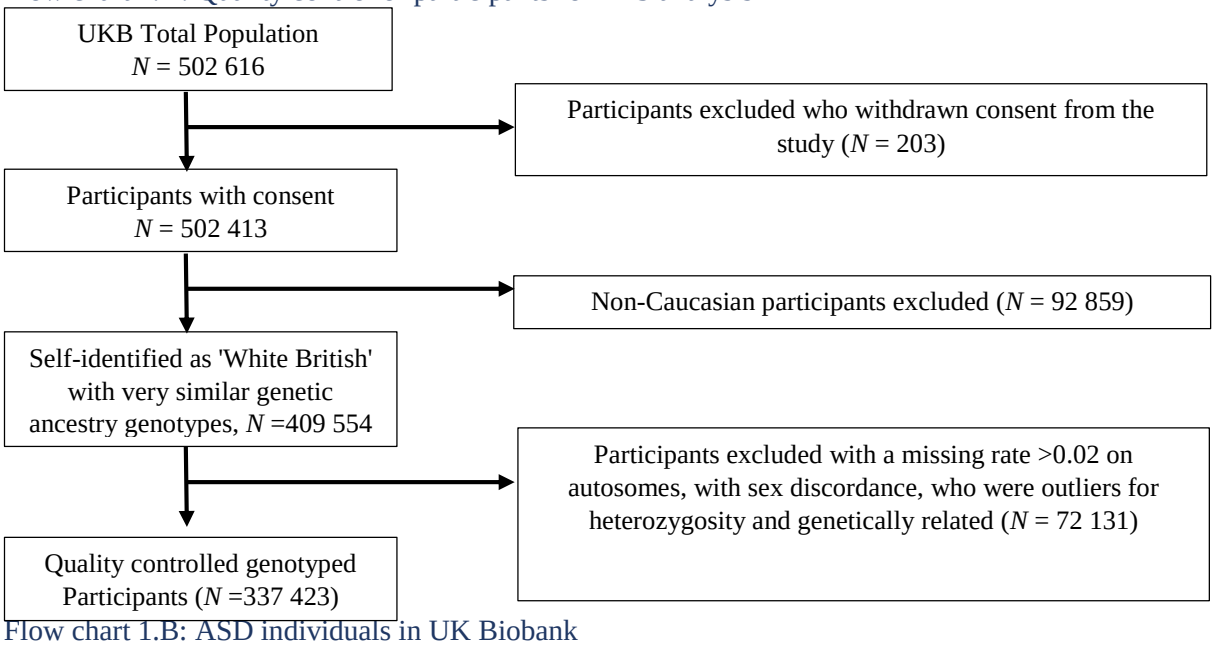
Supplementary Material: Project I

Supplementary Table S1: Number and percentage of missing values for outcome variables.

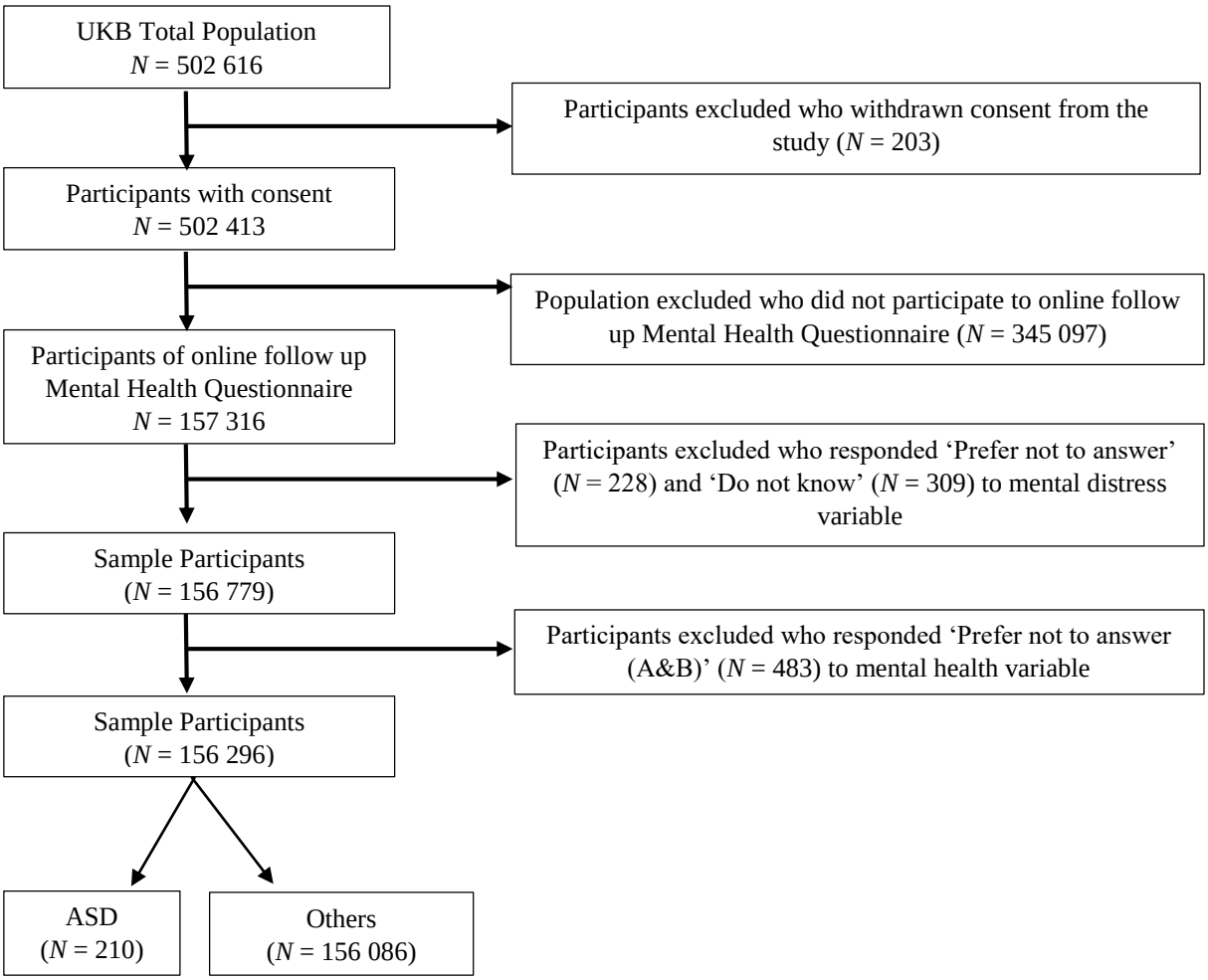
	n Valid	n Missing	% Missing
Employment status	108 711	0	0
Age	34 808	0	0
Sex	34 808	0	0
Education	34 808	0	0
TDI	34 733	75	0.2
BMI	34 706	102	0.3
Physical Activity (MET Score)	28 292	6 516	18.7
Neuroticism	29 706	5 102	14.7
Work Hours (Per Week)	34 322	486	1.4
Job Satisfaction	34 808	0	0
Job Tenure (Years)	34 712	96	0.3

Supplementary Material: Project II

Flow chart 1.A: Quality control of participants for PRS analysis



Flow chart 1.B: ASD individuals in UK Biobank



Supplementary Table 1: WBS traits analysis among identified ASD individuals in UKB

	ASD	Other	*P*
Neuroticism			
N	158	130 489	
Mean ± SD	6.65±3.5	3.86±3.2	
β (95%CI)	2.9 (2.4 to 3.3)		$8.3x10^{-31}$
Loneliness			
N	199	154 182	
Mean ± SD	0.44±0.4	0.16±0.4	
OR (95%CI)	4.45 (3.4 to 5.9)		$3.4x10^{-25}$
Depression			
N	206	155 336	
Mean ± SD	0.69±0.5	0.33±0.47	
OR (95%CI)	5.9 (4.3 to 7.9)		$8.2x10^{-31}$
Positive Affect			
N	67	57 769	
Mean ± SD	3.73±0.93	4.46±0.69	
β (95%CI)	-0.7 (-0.9 to -0.5)		$1.5x10^{-16}$
Life satisfaction			
N	43	41 517	
Mean ± SD	3.88±0.89	4.5±0.54	
β (95%CI)	- 0.6 (-0.8 to -0.4)		$4.9x10^{-13}$

This table provides the detailed results obtained from UKB participants responded to 'Mental Health problems ever diagnosed by a professional' questionnaire (Data field 20544); ASD, Autism Spectrum Disorder; Others, Reference as non-ASD; *P*, significance for concerned analysis. Values expressed as *N*, Number of participants; *SD*, Standard deviation; *β*, regression coefficient (unstandardized); *CI*, Confidence interval; *OR*. Odds ratio.

*Equal variance assumed

**Unstandardized coefficients reported

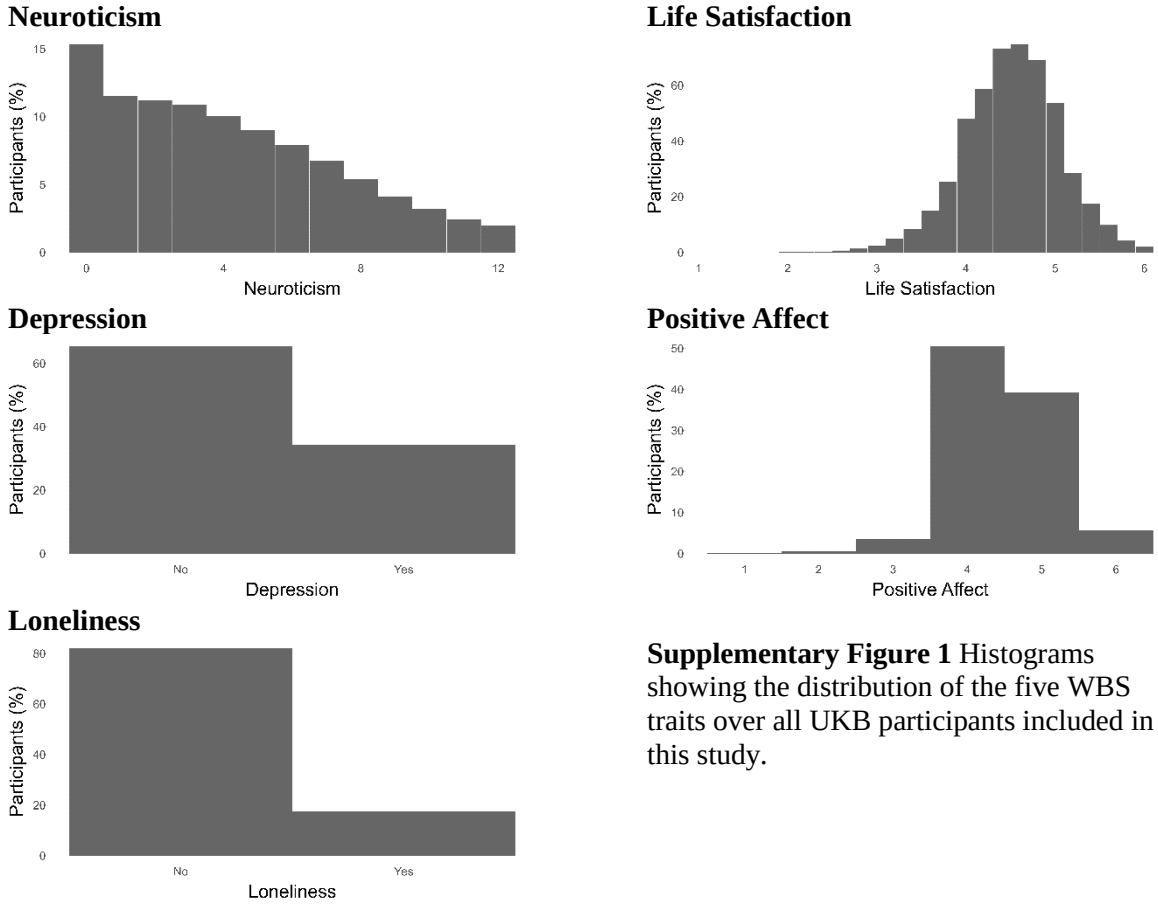
Supplementary Table 2: Prediction of PRS for autism across the 5-WBS traits

Traits	pT	R^2 (%)	β	SE	*P* *	SNPs, *n*	AUC
Neuroticism	0.07625	0.04	655.9	59.6	3.8×10^{-28}	20504	0.51
Depression	0.404	0.06	965.2	79.0	2.9×10^{-34}	60844	0.51
Loneliness	0.01545	0.04	195.3	22.2	1.4×10^{-18}	6648	0.51
Life satisfaction	0.0009	0.08	-21.2	2.8	4.3×10^{-14}	853	0.56
Positive affect	0.2924	0.10	-402.1	38.4	1.3×10^{-25}	50192	0.53

This table provides the result of the high resolution best-fit polygenic risk score analyses of autism for the five well-being traits. We report here the p value threshold (pT) and variance (R^2) in percentage (%) of most predictive model in addition to unstandardized regression coefficient (β) and standard error (SE). SNP, single nucleotide polymorphism. AUC, area under the receiver operating characteristics (ROC) curve.

*The Empirical *P*-value found 1×10^{-4} for all the traits and considered for significance threshold.

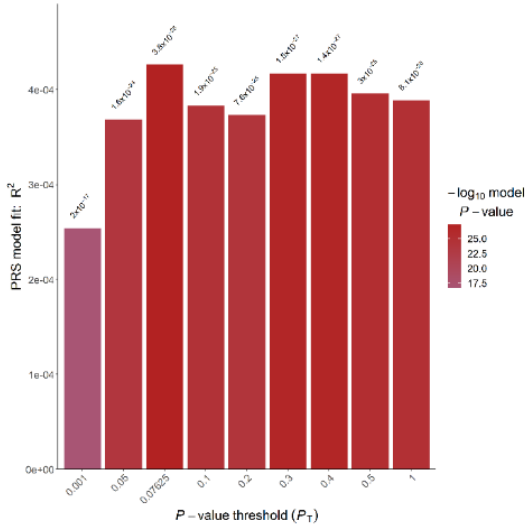
Supplementary Figure 1: Histograms of five primary phenotypes



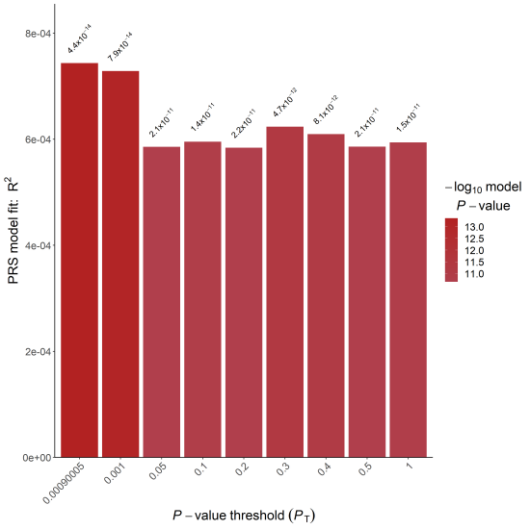
Supplementary Figure 1 Histograms showing the distribution of the five WBS traits over all UKB participants included in this study.

Supplementary Figure 2: Association between ASD PRS and target traits

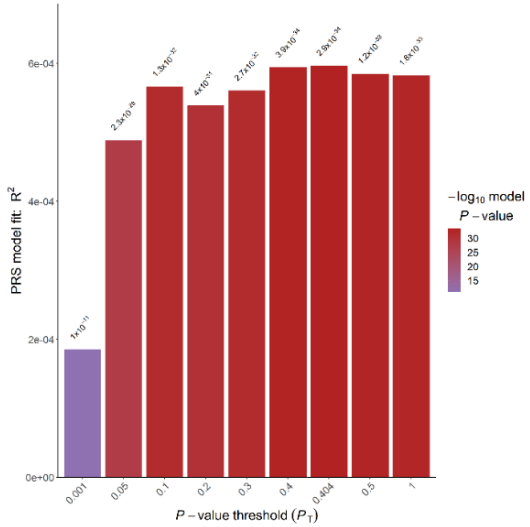
Neuroticism



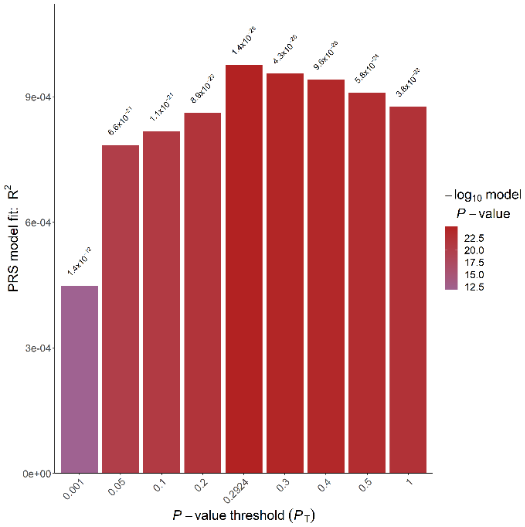
Life Satisfaction



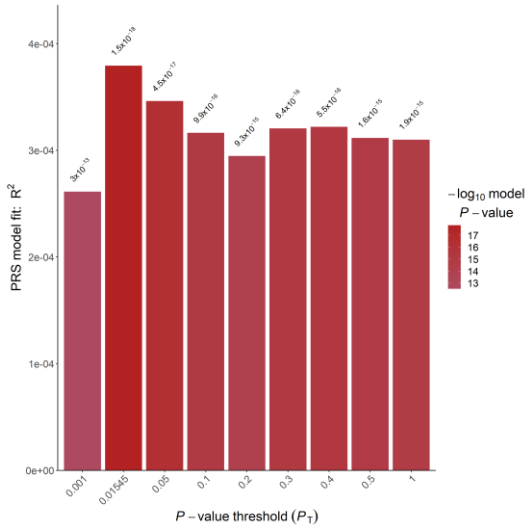
Depression



Positive Affect



Loneliness



Supplementary Figure 2. Association between polygenic risk scores for ASD and target traits. Values on top of the bars represent *P*-values for the regression models. The Empirical *P*-value found $1x10^{-4}$ for all the traits and considered for significance threshold. All the models on different thresholds show significant association. *Represent the 'best fit' model explaining maximum variance.