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Polygenic liabilities underlying job stress and exhaustion over a 10-year follow-up: A general population study

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ABSTRACT

We investigated whether individuals, who have a high polygenic loading for schizophrenia and major depression (PGL) but have not developed the respective disorders, are still susceptible to experience milder forms of ill-being in terms of job strain or exhaustion. We used the population-based Young Finns Study data ($n = 928$). PGL was assessed with a cumulative score of the polygenic risk scores for schizophrenia and depression. Participants (24–49-year-olds) evaluated their exhaustion levels and perceived job characteristics over a 10-year follow-up (2001, 2007, 2011). Participants with diagnosed psychotic or affective disorders were excluded. We found that high PGL did not predict less favorable perceptions of job environment (job strain, demands, control, satisfaction, social support at work) but high PGL predicted a higher trajectory of exhaustion in early adulthood and middle age. Additionally, high (vs. low) PGL predicted a stronger increase in exhaustion at increased levels of job strain. These findings remained after controlling for sex, socioeconomic factors, health behaviors, and cognitive performance. In conclusion, individuals with high PGL may have an elevated liability to experience exhaustion especially in early adulthood and middle age (despite they perceive their job environment similarly than others), and especially and at high levels of job strain.

1. Introduction

Within the field of psychiatric genetics, two viewpoints have been emphasized most recently. First, an increasing attention has been directed to "cross-disorder" polygenic risk scores, i.e., combinations of polygenic risks for two or more psychiatric disorders (Schmitt et al., 2021). This is because the accuracy of polygenic risk scores in predicting specific mental disorders is quite low (Consortium, 2014; Ripke et al., 2013). For example, high polygenic risk for schizophrenia predicts a higher likelihood of non-affective psychoses, but also predicts a higher likelihood of affective disorders (Musliner et al., 2019; Richards et al., 2019), explains variation in depressed patients' clinical outcomes (Fanelli et al., 2021), and correlates positively with trait anxiety (Hatzimanolis et al., 2018). High polygenic risk for depression, in turn, relates to increased likelihood of depression but also schizophrenia (Mistry et al., 2018). Additionally, a recent study in a clinical sample, for example, showed that using a "cross-disorder" polygenic risk for schizophrenia and depression improved accuracy when predicting patients' treatment responses (Schubert et al., 2021). Given this evidence, the present study investigated long-term trajectories of individuals with

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"cross-disorder" polygenic psychiatric risk for schizophrenia and depression.

Second, an emerging trend is to investigate which other kinds of outcomes do polygenic risks predict than the respective psychiatric diagnoses. Increasingly, emphasis is directed to developmental trajectories of such individuals who have a disorder-susceptible genotype but have *not* developed the phenotype (disorder). Those individuals are a notable part of population: ca. 40% and 90–91% of offspring of parents with mood disorder or schizophrenia, respectively, do *not* develop the disorder (Beardslee et al., 1998; Gottesman et al., 2010; II., 1991). In accordance with this, it has been found that polygenic risk scores explain quite a minor portion of the liability to the disorders: a polygenic risk score for schizophrenia or depression explains ca. 7.7% or 10% of variation of the likelihood of having schizophrenia or depression diagnosis (Howard et al., 2018; Legge et al., 2021), respectively. Accordingly, a recent review pointed out that "polygenic risk scores will never be able to establish or definitively predict a diagnosis of common complex conditions (eg, mental health disorders)" (Murray et al., 2021). Thus, the present study aims to investigate whether high polygenic risk for schizophrenia and major depression predicts other trajectories of ill-being among those who have not developed the disorder.

Recently, the association of polygenic risk for psychiatric disorders with work-related strain has received attention. Current evidence suggests that a high polygenic risk for schizophrenia predicts lower educational levels and weaker labor market outcomes (Viinikainen et al., 2022), and high polygenic risk for depression relates to reduced school attainment (Amin et al., 2021). The studies did not, however, separate individuals with vs. without the disorder when investigating socioeconomic outcomes. Thus, it has remained unclear whether polygenic risk for psychiatric disorders predicts harmful socioeconomic trajectories also among those not developed the disorder, or only among those diagnosed with the disorder. The disorder-related burden in working life is well-known: as much as 50% of schizophrenia patients develop disability pension over a 5-year follow-up (Kiviniemi et al., 2011), 54% of them have a poor working ability (Lauronen et al., 2007), 29% of them have lost their productivity (Evensen et al., 2016), and only around 10% of working-aged patients are employed (Evensen et al., 2016). Among depression patients, in turn, as many as 21% are unemployed (Amiri, 2021), 68% of them develop disability pension (Amiri and Behnezhad, 2019), and 20% of them experience job turnover over a 6-month follow-up (Lerner et al., 2004). Taken together, evidence is lacking whether a polygenic risk for psychiatric disorders predicts liability to experience work-related strain also among those not developed the disorders.

The present study investigated whether a cross-disorder polygenic risk for schizophrenia and major depression (PGL) predicts deviant trajectories of perceived job strain and exhaustion among those not developed the disorders. We used the population-based Young Finns data with a 10-year prospective follow-up of perceived job characteristics and exhaustion (participants being 24–49-year-olds). The data provided possibilities for taking into consideration a variety of potential confounders such as socioeconomic factors, health behaviors, and cognitive performance.

2. Method

2.1. Participants

The participants come from the Young Finns Study (YFS) that is an on-going prospective follow-up study. The YFS started in 1980 (baseline study) and the participants have been followed since then. The sampling was designed to include a population-based sample of non-institutionalized Finnish children, representative with regard to sex (male vs. female), rural vs. urban environment, and Eastern vs. Western regions in Finland. The sample consisted of six age cohorts (born in 1962, 1965, 1968, 1971, 1974, or 1977). The sampling was conducted in the Finnish universities with medical schools (i.e., Universities of Helsinki, Turku, Tampere, Oulu, and Kuopio). Participants were invited from the university cities (50%) and from surrounding rural municipalities (50%). Such rural municipalities were selected that were within 200 km distance from the respective university, had an approximately similar industrial structure, and included a sufficient number of children belonging to the investigated age cohorts. A total of 4320 subjects were invited, and 3596 of them participated in the baseline measurement. Additional information can be found elsewhere (Raitakari et al., 2008).

In this study, we first excluded all the subjects who had not been genotyped ($n = 1153$), who had been diagnosed with non-affective psychotic disorders or affective disorders ($n = 112$), or who reported not working outside home over the follow-up (2001, 2007, 2011) ($n = 1236$). Thereafter, we excluded subjects who did not have data available on exhaustion, job environment, or health behaviors in any follow-up year (2001, 2007, 2011) ($n = 46$); or did not have data available on participants' (2011) or their parents' (1980) socioeconomic factors ($n = 105$). Thus, the final sample size of the present study was 928 participants.

The study design has been approved by the ethical committees of all Finnish Universities with a medical faculty. All the participants or their parents (participants aged < 18 years) provided informed consent before participation. The YFS has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

The Cardiovascular Risk in Young Finns (YFS) dataset comprises health related participant data and their use is therefore restricted under the regulations on professional secrecy (Act on the Openness of Government Activities, 612/1999) and on sensitive personal data (Personal Data Act, 523/1999, implementing the EU data protection directive 95/46/EC). Due to these legal restrictions, the data from this study cannot be stored in public repositories or otherwise made publicly available. However, data access may be permitted on a case-by-case basis upon request. Data sharing outside the group is done in collaboration with YFS group and requires a data-sharing agreement. Investigators can submit an expression of interest to the chairman of the publication committee (Prof. Mika Kähönen, Tampere University, Finland).

2.2. Measures

2.2.1. Polygenic risk for schizophrenia and major depression (PGL)

Polygenic risk score for schizophrenia was calculated on the basis of the summary statistics of the most recent genome-wide association study (GWAS) on schizophrenia that was conducted by Schizophrenia Working Group of the Psychiatric Genomics Consortium et al. and published in Nature (Consortium, 2014). Specifically, a weighted polygenic risk score (Igo et al., 2019) for every study subject was created by summing up each participant's schizophrenia-associated risk alleles weighted by risk allele beta estimates (Consortium, 2014). Altogether 128 independent SNPs reaching genome-wide significance in the schizophrenia GWAS were included in the PRS. More specifically, genotyping was done for 2 556 samples using custom build Illumina Human 670k BeadChip at Welcome Trust Sanger Institute. Sample call rate < 0.95, excess heterozygosity, sex mismatch, cryptic relatedness (pi-hat > 0.2), SNP call rate ⟨ 0.95, MAF < 0.01, and HWE p-value < 1e-6 were used as quality control filters. After the quality control, there were 2 443 samples and 546 677 genotyped SNPs available for further analysis. Genotype Imputation to 1 000 Genomes reference was performed using SHAPEIT v1 for haplotype phasing and IMPUTE2 and 1 000 Genomes March 2012 haplotypes for genotype imputation. SNPs with imputation information metric ⟩ 0.3 were considered as well-imputed. This polygenic risk score for schizophrenia has been used previously (Saarinen et al., 2022).

Polygenic risk score for depression. Genomic DNA was extracted from peripheral blood leukocytes using a commercially available kit and Qiagen BioRobot M48 Workstation according to the manufacturer's instructions (Qiagen, Hilden, Germany). Genotyping was done for 2556 samples using custom build Illumina Human 670 k BeadChip

atWelcome Trust Sanger Institute. Genotypes were called using Illuminus clustering algorithm. Samples that failed Sanger genotyping pipeline QC criteria (i.e., duplicated samples, heterozygosity, low call rate, or Sequenom fingerprint discrepancy) were excluded from analysis. Similarly, samples with sex discrepancy, low genotyping call rate (< 0.95) and possible relatedness (pi-hat > 0.2) were excluded from the analysis. Short Nucleotide Polymorphisms (SNPs) were excluded based on Hardy-Weinberg equilibrium test ($p \leq 1e\text{-}06$), failed missingness test (call rate < 0.95) and failed frequency test (minor allele frequency < 0.01). After quality control, 546,677 genotyped SNPs were available for further analysis. Genotype imputation was performed using Minimac3 (Das et al., 2016) and 1000 G phase3 reference set on Michigan Imputation Server. A total of 102 depression related SNPs identified using genomic data from >800,000 individuals (p-value $< 5 \times 10^{-8}$) by (Howard et al., 2019) were used for calculation of weighted genetic risk score (GRS) for depression using Plink software (Purcell et al., 2007).

Polygenic risk for schizophrenia and depression (PGL) was calculated as the sum score of polygenic risk scores for schizophrenia and depression. That is, both scores were first standardized (mean = 0, $SD = 1$) and then summed together. The correlation between the polygenic risk scores for depression and schizophrenia was low ($r = 0.079$, $p < 0.05$).

2.2.2. Psychiatric diagnoses

In this study, we excluded participants with non-affective psychoses or affective disorders having required hospital care. Participants' psychiatric diagnoses over their lifespan were collected up to 2017 (when participants were 40–55 years old) from the Care Register for Health Care (https://thl.fi/en/web/thlfi-en/statistics-and-data/data-and-services/register-descriptions/care-register-for-health-care). In the hospital register, diagnoses were given in line with the prevailing diagnostic classification at that time (ICD-8, ICD-9, or ICD-10). The conversion of ICD-diagnoses to DSM-IV diagnoses has been described elsewhere (Sormunen et al., 2017). Diagnoses were categorized into the following groups: non-affective psychotic disorders, affective disorders (mood and anxiety disorders), substance-related disorders, and personality disorders. Participants with several diagnoses were classified into one group in this priority order: non-affective psychoses (DSM-IV 295, 297–298), personality disorders (DSM-IV 301), affective disorders (mood and anxiety disorders, DSM-IV 296, 300, 311), and substance-related disorders (DSM-IV 291–292, 303–305). The register has been used also in previous research (Suvisaari et al., 1999).

2.2.3. Exhaustion

Exhaustion was measured with The Maastricht Vital Exhaustion Questionnaire (MQ) (Appels et al., 1987) that includes 21 items related to e.g. pervasive fatigue, sleep disturbances, reduced level of functioning (e.g., reduced ability to solve problems), somatic symptoms, and death wishes (e.g. "Do you ever wake up with a feeling of exhaustion and fatigue?"; "Do you feel you want to give up trying?") that are responded with a three-point scale (0 = no; 1 = I'm not sure; 2 = yes). The MQ had good internal consistency (Cronbach's α = 0.86–0.88 in 2001–2011). We calculated the mean score of the items for all the participants who had responded to at least 50% of the items. High scores of MQ are found to correlate with physiological and psychological stress measures: altered cardiac reactivity to task-induced stress (Keltikangas-Järvinen and Heponiemi, 2004), decreased habituation of free cortisol responses to repeated acute psychosocial stress (Kudielka et al., 2006), and altered cortisol levels and higher perceived stress (Nicolson and van Diest, 2000).

Since many studies have reported moderate-to-high correlations between the MQ and depression (Kop et al., 1998), the differences/similarities between the two concepts have been discussed. An early work reported that most evident symptoms of exhausted subjects are loss of vigor and excess fatigue (rather than emotional symptoms) (van Diest and Appels, 1991). Later on, factor analyses have shown that the MQ items and items of depression scales are loaded on different factors (Kudielka et al., 2004; Vroege et al., 2012). Also, a review (Suls and Bunde, 2005) stated that vital exhaustion and depression are not synonymous since vital exhaustion does not include feelings of worthlessness, sadness, or guilt that are common in depression. In addition, there is evidence that vital exhaustion is a stronger predictor of cardiovascular conditions (Balog et al., 2017) or inflammation in cardiovascular conditions (Janszky et al., 2005) than depression. Regarding cognitive performance, vital exhaustion seems to be related to cognitive impairments at milder levels than depression (Ketvel et al., 2023). Hence, vital exhaustion seems to be more strongly related to stress-related physiological conditions and cognitive impairments than depression.

Also, there has been discussion on the conceptual relations between vital exhaustion and burnout. Burnout is commonly conceptualized as feelings of energy depletion (exhaustion), cynicism related to one's job, and feelings of reduced professional efficacy (reduced occupational self-esteem) (Maslach, 2021). Although the MQ does not include items directly related to work, the MQ correlates strongly with burnout scales ($r = 0.68$) (Lerman et al., 1999), work stress (Schnorpfeil et al., 2002), and work overcommitment (Preckel et al., 2005). Also, it seems that the MQ correlates most strongly with the burnout dimensions of emotional exhaustion and career dissatisfaction (Bellingrath et al., 2008). In this study, we included only participants who were full-time workers to focus on exhaustion of the employed population.

2.2.4. Perceived job characteristics

Job demands were assessed in 2001, 2007, and 2011 with a three-item questionnaire derived from the Occupational Stress Questionnaire (Elo et al., 1992) developed by the Finnish Institute of Occupational Health and validated in 25 000 Finnish employees. The items ("Does your work have phases that are too difficult?") were responded with a 5-point scale (1 = totally disagree, 5 = totally agree). We calculated a total score of the items for each measurement year. Single items had strong correlations with the mean score ($r = 0.69$–0.77 in 2001; $r = 0.68$–0.80 in 2007; and $r = 0.72$–0.78 in 2011), indicating good internal consistency.

Job control was assessed in 2001, 2007, and 2011 with nine items from the Job Content Questionnaire (Karasek, 1985) (e.g., "I can make many independent decisions at work"). The items were responded with a 5-point scale (1 = totally disagree, 5 = totally agree). The scale had good internal reliability (Cronbach's α = 0.85–0.86 in 2001, 2007, and 2011).

Job strain was calculated as recommended in Karasek's model, i.e., as the ratio of job demand to job control (job demand/job control). That is, job strain refers to a combination of high job demands combined and low job control. It has been recommended to use a continuous measure and to equally weigh job demands and job control when assessing job strain (Landsbergis et al., 1994; MacCallum et al., 2002).

Social support at work was assessed in 2001, 2007, and 2011 by asking participants whether they receive help and support from their employer if needed (1 = very much, 5 = very little) and what kind of social relationships do they have with their colleagues (1 = very good, 5 = very bad). We calculated a total score of the items for 2001, 2007, and 2011.

Job satisfaction was assessed in 2001, 2007, and 2011 by asking the participants how satisfied they are with their job (1 = very dissatisfied, 5 = very satisfied).

Working hours were assessed in 2001, 2007, and 2011 by self-reports filled by the participants (1 = regular working hours, 2 = shift work, 3 = evening or night work, 4 = irregular working hours). We formed a dichotomous variable with a value of 0 (regular working hours, response option 1) or 1 (irregular working hours, response options 2–4).

2.2.5. Covariates

Other covariates included participants' (2011) and their parents' (1980) socioeconomic factors (educational level, occupational status, level of income); health behaviors in 2001, 2007, and 2011 (smoking, alcohol consumption, physical activity); and cognitive performance in

2011 (visual memory, spatial working memory, reaction time, sustained attention). A more detailed description of their measurement is available in Supplementary Methods. Health behaviors and cognitive performance were controlled for as polygenic risk for schizophrenia is found to correlate with cognitive capacity (Engen et al., 2020) and health behaviors (Wang et al., 2020).

2.3. Statistical analyses

First, we excluded the participants who had been diagnosed with non-affective psychotic disorders or affective disorders (until 2017), or reported not working outside home over the follow-up (2001, 2007, 2011). Then, we investigated attrition over the follow-up using independent samples t-tests or chi-square tests.

Next, we examined whether individuals with high polygenic risk for schizophrenia and major depression (PGL) are prone to end up in less favorably perceived job environments. For this purpose, we used growth curve models (with maximum likelihood estimation). We predicted the curves of perceived job characteristics (i.e., perceived job strain, job demands, job control, job satisfaction, social support at work) over the 10-year follow-up (2001, 2007, 2011). The scores of the perceived job characteristics were standardized with year 2001 mean and standard deviation to stabilize the growth curve. PGL was set as the predictor variable.

Thereafter, we examined whether PGL predicts the curve of exhaustion over the 10-year follow-up (2001, 2007, 2011) using growth curve modeling (maximum likelihood estimation). Similarly to the former analyses, exhaustion scores were standardized with year 2001 mean and standard deviation to stabilize the growth curves. PGL was set as the predictor variable.

Finally, we investigated whether job strain predicts exhaustion differently in individuals with higher (vs. lower) PGL; i.e., whether PGL moderates the association of job strain trajectory with exhaustion trajectory. We added the interaction term between PGL and job strain to the model, when predicting the curve of exhaustion over the 10-year follow-up. We also included a squared score of job strain in the model, in order to consider a curvilinear effect of job strain on exhaustion.

The analyses were run with step-wisely added control variables. Model 1 was adjusted for age, age-squared, and sex; Model 2 also for participants' and their parents' socioeconomic factors (educational level, annual income, occupational status); Model 3 also for perceived job characteristics over the follow-up (i.e., perceived job demands, job control, job satisfaction, irregular working hours, and social support at work); Model 4 also for health behaviors over the follow-up (physical activity, alcohol consumption, and daily smoking status); and Model 5 also for cognitive performance (an additional sensitivity analysis). As there were no significant sex-PGL interactions when predicting perceived job characteristics or exhaustion, the analyses were run for both sexes simultaneously.

3. Results

Descriptive statistics of the main study variables are shown in Table 1 and for other covariates in Supplementary Table 2. The results of attrition analyses are presented in Supplementary Table 3. To summarize, there was no consistent attrition bias in sex, PGL, educational level or occupational status in adulthood, job demands, job satisfaction, or type of working hours (regular or non-regular). Included participants were, however, slightly older (ca. one year), had slightly lower exhaustion scores, higher perceived job control, slightly lower job strain, and slightly higher annual income than dropped-out participants.

3.1. PGL predicting the curves of perceived job characteristics

First, we examined whether PGL predicts the curves of job characteristics over the 10-year follow-up. Table 2 shows the results when adjusted for age, sex, socioeconomic factors, and health behaviors. PGL did not predict perceived job strain, job control, job demand, job satisfaction, or social support at work. There were no significant age-interactions (or age-squared interactions) with PGL when predicting job characteristics, indicating that the association of PGL with job

Table 1
Descriptive statistics of the main study variables.

	Mean (*SD*)	Frequency (%)	Measurement range
Age (2001)	32.16 (4.98)		
Sex (Female)		478 (51.5)	
PGL	−0.07 (1.51)		min = −4.53, max = 4.41[1]
Exhaustion			
2001	0.47 (0.33)		0–2
2007	0.47 (0.36)		0–2
2011	0.47 (0.37)		0–2
Job strain			
2001	0.77 (0.26)		min = 0.20, max = 3.00[1]
2007	0.80 (0.24)		min = 0.25, max = 2.75[1]
2011	0.80 (0.23)		min = 0.28, max = 2.14[1]
Job demands			
2001	2.87 (0.66)		1–5
2007	2.95 (0.63)		1–5
2011	2.96 (0.65)		1–5
Job control			
2001	3.86 (0.69)		1–5
2007	3.82 (0.67)		1–5
2011	3.83 (0.64)		1–5
Job satisfaction			
2001	3.90 (0.85)		1–5
2007	3.77 (0.92)		1–5
2011	3.76 (0.95)		1–5
Social support at work			
2001	3.77 (0.81)		1–5
2007	3.79 (0.80)		1–5
2011	3.78 (0.85)		1–5
Non-regular working hours			
2001		316 (34.1)	
2007		304 (32.8)	
2011		279 (30.1)	
Educational level (2011)			
Comprehensive school		15 (1.6)	
Occupational school or high school		206 (22.2)	
Academic level		707 (76.2)	
Occupational status (2011)			
Manual worker		181 (19.5)	
Lower-grade non-manual worker		345 (37.2)	
Upper-grade non-manual worker		402 (43.3)	
Annual income (2011)	7.97 (2.76)		1–13

[1] A continuous score without a predefined scale. PGL = Polygenic risk for schizophrenia and major depression.

Table 2
Results of growth curve models. Estimates (B) with standard errors (SE) of PGL, when predicting standardized scores of perceived job characteristics in adulthood.

	Job strain			Job control			Job demands			Job satisfaction			Social support at work		
	B	*SE*	*p*	B	*SE*	*P*	B	*SE*	*p*	B	*SE*	*p*	B	*SE*	*p*
Fixed effects															
Intercept	−0.467	0.469	0.320	−1.641	0.432	< 0.001	−2.229	0.515	< 0.001	0.702	0.618	0.256	−0.483	0.566	0.393
PGL	0.022	0.015	0.138	−0.008	0.016	0.592	0.026	0.017	0.123	−0.028	0.016	0.083	−0.008	0.017	0.639
Random effects															
Variance of intercept	0.546	0.021	< 0.05	0.607	0.020	< 0.05	0.630	0.023	< 0.05	0.439	0.031	< 0.05	0.550	0.026	< 0.05
Residual variance	0.629	0.012	< 0.05	0.556	0.011	< 0.05	0.686	0.013	< 0.05	0.899	0.017	< 0.05	0.783	0.015	< 0.05

$n = 921$.
Note: "Fixed effects" refer to the classic regression coefficients. "Random effects" refer to between-individual variation in the intercept and residual variance. The models reported here were adjusted for sex, participants' and their parents' socioeconomic factors, and participants' health behaviors.

characteristics remained non-significant over age (between the ages of 24–39 years).

The effect of PGL on perceived job characteristics remained non-significant also in the other models: when adjusted only for age and sex; or when adjusted only for age, sex, and socioeconomic factors; or when adjusted also for cognitive performance. Taken together, individuals with high (vs. low) PGL were found to be working in approximately similarly perceived job environments.

3.2. PGL predicting the curve of exhaustion

Next, we examined whether PGL predicts the curve of exhaustion over the 10-year follow-up. The results are presented in Table 3. PGL had a positive main effect on exhaustion when adjusted for age and sex (Model 1, $p = 0.024$), when adjusted also for socioeconomic factors (Model 2, $p = 0.019$), when adjusted also for job characteristics (Model 3, $p = 0.010$), when adjusted also for health behaviors (Model 4, $p = 0.035$), and when adjusted also for cognitive performance (Model 5, $p = 0.032$). Additionally, we found significant age-interactions with the PGL ($p = 0.006$–0.024 in Models 1–5), indicating that the association changed linearly over age. Also, we found significant age squared-interactions with the PGL ($p = 0.003$–0.014 in Models 1–5), indicating that the association of PGL with exhaustion changed also curvilinearly over age.

The findings are illustrated in Fig. 1. Taken together, in individuals with low/average PGL, the curve of exhaustion slightly decreased over age from early adulthood to middle age. Individuals with high PGL, in turn, had higher scores of exhaustion (than expected for their age) in early adulthood and in middle age (after the age of ca. 40 years). These findings sustained after controlling for sex, participants' and their parents' socioeconomic factors, participants' job characteristics, health behaviors, and cognitive performance.

As sensitivity analyses, we reran the analyses with a square-root transformed variable of exhaustion as the distribution of exhaustion was slightly positively skewed in this non-clinical sample. The results remained (see Supplementary Figure 1 for illustration).

Finally, as additional analysis, we investigated whether PGL could select individuals into less favorable working conditions. For that purpose, we investigated associations of PGL with self-reported type of working time (regular day-time work, evening work, night work, shiftwork with two or three shifts, or irregular working time), occupational status (manual worker, lower-grade non-manual worker, upper-grade non-manual worker, farmer, entrepreneur), and duration of working days in hours (1–14 h or more) in 2011. We used both variance analysis and linear regression analysis. We found that PGL was not associated with type of working time ($p = 0.86$), occupational status ($p = 0.60$), or duration of working days in hours ($p = 0.45$). Thus, the findings indicated that individuals with high PGL were not more likely to end up in working conditions with e.g. longer working hours, shiftwork, or manual work.

3.3. PGL moderating the association of job strain with exhaustion

Finally, we investigated whether job strain predict exhaustion

Table 3
Results of growth curve models. Estimates (B) with standard errors (SE) of PGL and age, when predicting the curve of exhaustion over a 10-year follow-up in adulthood.

	Exhaustion														
	Model 1 ($n = 928$)			Model 2 ($n = 928$)			Model 3 ($n = 928$)			Model 4 ($n = 921$)			Model 5 ($n = 803$)		
	B	*SE*	*p*	B	*SE*	*p*	B	*SE*	*p*	B	*SE*	*p*	B	*SE*	*p*
Fixed effects															
Intercept	−0.649	0.403	0.107	−0.116	0.436	0.791	0.153	0.418	0.714	0.322	0.443	0.467	0.359	0.474	0.449
Age	0.021	0.022	0.329	0.021	0.022	0.332	0.000	0.021	0.986	−0.006	0.021	0.767	−0.008	0.023	0.739
Age squared	0.000	0.000	0.329	0.000	0.000	0.336	0.000	0.000	0.865	0.000	0.000	0.854	0.000	0.000	0.801
PGL	0.623	0.276	**0.024**	0.647	0.275	**0.019**	0.676	0.262	**0.010**	0.561	0.266	**0.035**	0.609	0.284	**0.032**
PGL*Age	−0.036	0.015	**0.018**	−0.037	0.015	**0.014**	−0.039	0.014	**0.006**	−0.033	0.014	**0.024**	−0.036	0.015	**0.019**
PGL*Age squared	0.001	0.000	**0.011**	0.001	000.0	**0.009**	0.001	0.000	**0.003**	0.000	0.000	**0.014**	0.001	0.000	**0.010**
Random effects															
Variance of intercept	0.659	0.021	< 0.05	0.646	0.021	< 0.05	0.553	0.020	< 0.05	0.548	0.020	< 0.05	0.527	0.021	< 0.05
Residual variance	0.614	0.011	< 0.05	0.613	0.011	< 0.05	0.581	0.011	< 0.05	0.571	0.011	< 0.05	0.580	0.012	< 0.05

Note: "Fixed effects" refer to the classic regression coefficients. "Random effects" refer to between-individual variation in the intercept and residual variance.
Model 1 was adjusted for age and sex.
Model 2 was adjusted also for participants' and their parents' socioeconomic factors.
Model 3 was adjusted also for job characteristics.
Model 4 was adjusted also for health behaviors.
Model 5 was adjusted also for cognitive performance.

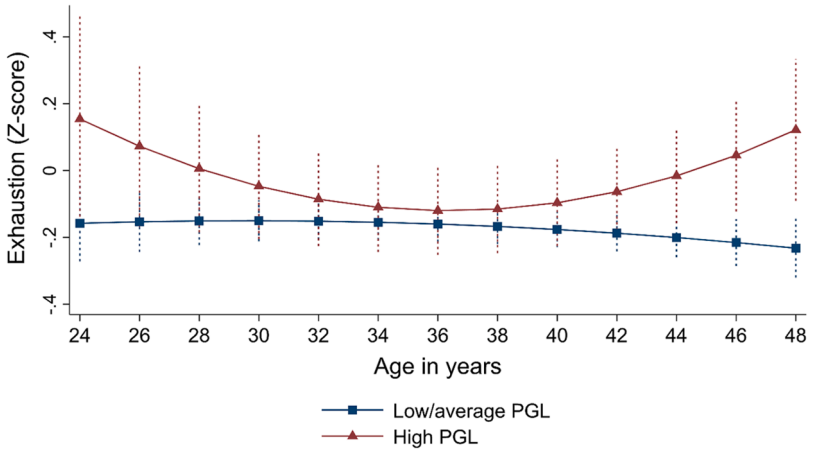

Fig. 1. Model-predicted values with 95% confidence intervals of exhaustion separately for subjects with low (−1 *SD*) or average PGL and for subjects with high (+ 1 *SD*) PGL.
Note: Adjusted for sex, participants' and their parents' socioeconomic factors, participants' job characteristics, and health behaviors.

differently in individuals with higher (vs. lower) PGL. The results with full details are presented in Supplementary Table 4. To summarize, we found a significant interaction effect between PGL and job strain when predicting exhaustion in all the models: in Model 1 (adjusted for age and sex, $p = 0.012$), in Model 2 (adjusted also for socioeconomic factors, $p = 0.008$), in Model 3 (adjusted also for health behaviors, $p = 0.009$), and in Model 4 (adjusted also for cognitive performance, $p = 0.028$). The finding indicates that, when perceived job strain increased, exhaustion levels increased more strongly in individuals with high (vs. low/average) PGL (see Fig. 2).

4. Discussion

This study examined whether individuals with a high polygenic risk for schizophrenia and major depression (PGL) and without the respective disorders are still susceptible to experience milder forms of ill-being in terms of job strain or exhaustion. We found that high PGL did not predict less favorable perceptions of job environment, i.e., individuals with high PGL did not experience excessive levels of job strain, job demands, job dissatisfaction, or lack or social support at work. Nevertheless, individuals with high PGL had on average a higher trajectory of exhaustion in early adulthood and middle age. Additionally, exhaustion increased as the function of job strain more strongly in individuals with high (vs. low) PGL. The findings suggest that, even if individuals with high polygenic risk for schizophrenia and major depression do not develop the respective psychiatric disorders, they may have an increased risk for exhaustion, especially in demanding work environments.

Previously, polygenic risk scores for mental disorders have been found to correlate with health behaviors (Wang et al., 2020) and cognitive capacity (Engen et al., 2020) that, in turn, are related to burnout (Kulikowski, 2021; Naczenski et al., 2017). In our study, the association of high PGL with higher exhaustion levels was not explained by adverse health behaviors (physical activity, alcohol consumption, smoking status) or poorer cognitive performance (visual memory, spatial working memory, reaction time, sustained attention). As polygenic risk scores include variants related to e.g. glutamatergic system and synaptic plasticity (Consortium, 2014), the mechanisms between PGL and exhaustion may relate to certain genetically determined

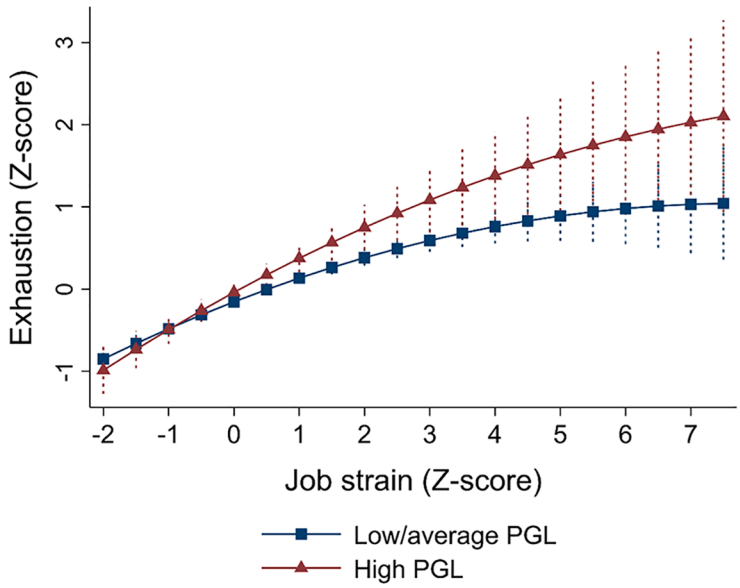

Fig. 2. Model-predicted values of exhaustion at different levels of job strain separately for subjects with low (−1 *SD*) or average PGL and for subjects with high (+ 1 *SD*) PGL.
Note: Adjusted for age, sex, participants' and their parents' socioeconomic factors, and participants' health behaviors.

alterations in the neurotransmitter systems and neural transmission.

We found that exhaustion increased as the function of job strain more strongly in individuals with high (vs. low) PGL. This interaction finding may not be explained by that individuals with high PGL might end up in unfavorably biased work conditions since PGL was not related to duration of working day in hours, occupational status, or working time (whether daytime work, shiftwork etc.). Second, our interaction finding may not be explained by a higher prevalence of severe affective or psychotic disorders in individuals with high PGL because we excluded participants who had developed such disorders. Since the PGL includes SNPs related to, for example, excitability of prefrontal neurons, inflammation and immune responses, mood modulation and emotion processing, synaptic functions, glutamatergic transmission (Consortium, 2014; Howard et al., 2019), we speculate that individuals with high PGL may have lower neuroinflammatory capacity to cope with stress and, thus, a higher likelihood of job strain evolving into exhaustion. Finally, there may be epigenetic mechanisms (outside the scope of this study) so that individuals with high PGL might be more susceptible to exhaustion-prone epigenetic changes under job strain.

While we examined polygenic liabilities (including hundreds of SNPs associated with depression and schizophrenia), previous studies have examined single genes and their interactions with environmental factors in the context of job strain. Specifically, life stress or occupational stress is reported to predict burnout most strongly in female carriers of the high expressing allele (MAO—H) (Plieger et al., 2019) or in carriers of rs41423247 and rs17209237 of the GCCR gene (Yi et al., 2022). Also, job strain is found to associate with early atherosclerosis in Val/Val-carriers of the COMT gene (Hintsanen et al., 2008) or in men with T/T genotype of Neuregulin-1 gene (Hintsanen et al., 2007) but not in others. In addition, high vital exhaustion is found to correlate with early atherosclerosis in men carrying G alleles of interleukin-6 gene (Chumaeva et al., 2014). Thus, it seems that gene-environment interactions play a substantial role in the development of exhaustion or burnout.

Our findings support a viewpoint that polygenic risks should not only be regarded as liabilities explaining the onset or course of a psychiatric disorder in clinical patient samples, but also as liabilities being present in non-clinical populations and having dynamic behavioral manifestations over the life course. That is, polygenic liabilities for psychiatric disorders are shown to predict increased risk for the phenotypes such as psychotic or depressive symptoms (Musliner et al., 2019; Richards et al., 2019), but also higher exhaustion proneness (as found in the present study) or higher creativity (Power et al., 2015) in the general population. Additionally, manifestations of the polygenic liabilities seem to be partly age-dependent: for example, polygenic risk for schizophrenia is associated with increased drop-out risk from primary school in adolescence (Sorensen et al., 2018) but higher magical thinking in middle age (Saarinen et al., 2022) in individuals without manifest psychosis.

Regarding limitations, there was some degree of participant drop-out over the follow-up. Included participants were slightly older and reported slightly lower exhaustion and job strain, and slightly higher perceived job control than dropped-out participants. The effect size of this attrition, however, was small (e.g., 32 vs. 31 years old). Additionally, it has been found to be unlikely that attrition would cause a notable bias to the results of prospective studies (Saiepour et al., 2019), and missing values of the Young Finns Study are found to be missing at random in psychological variables (Pulkki-Råback et al., 2015). Also, there was no attrition bias in most key variables (such as PGL, job demands, job satisfaction).

Second, psychiatric diagnoses were derived from the Care Register for Health Care, covering severe psychiatric disorders that have required hospital care. As patients with non-affective psychoses need hospital care in almost all cases, the register covers as much as 93% of schizophrenia-spectrum psychoses and 97% of psychotic disorders (Sund, 2012). Regarding affective disorders (mood and anxiety disorders), the register covers only the most severe cases having required hospital care.

Traditionally, origins of exhaustion in working-aged populations have been sought from work environment, including factors such as low job control, high demands, and lack of social support (Aronsson et al., 2017). A Cochrane Review concluded, however, that organizational interventions focused on changing working conditions were not effective, whereas cognitive-behavioral training and mental relaxation reduced stress effectively (Ruotsalainen et al., 2015). Our findings suggest that individuals with high PGL may be susceptible to experience exhaustion even if they perceive their work environment as favorable as those with lower PGL. Thus, our study tentatively implies that, in some cases, individuals with genetic liabilities may not benefit from organizational interventions targeting at job conditions (such as increasing social support at work) but might benefit from individually tailored exhaustion-reduction interventions.

Author statement

All the authors contributed to the conception or design of the study. J.H., S.R., M.K., J.V., O.R., T.L., and L.-K.J. contributed to data collection. A.S., L.-P.L. and B.H.M. contributed to data analyses. A.S. wrote the initial draft of the manuscript, and all the authors contributed to commenting and writing the manuscript and to interpreting the results.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2023.115355.

References

Amin, V., Behrman, J.R., Fletcher, J.M., Flores, C.A., Flores-Lagunes, A., Kohler, H.P., 2021. Genetic risks, adolescent health, and schooling attainment. Health Econ. 30 (11), 2905–2920.

Amiri, S., 2021. Unemployment associated with major depression disorder and depressive symptoms: a systematic review and meta-analysis. Int. J. Occup. Saf. Ergon. 1–13.

Amiri, S., Behnezhad, S., 2019. Depression and risk of disability pension: a systematic review and meta-analysis. Int. J. Psychiatry Med., 91217419837412

Appels, A., Höppener, P., Mulder, P., 1987. A questionnaire to assess premonitory symptoms of myocardial infarction. Int. J. Cardiol. 17 (1), 15–24.

Aronsson, G., Theorell, T., Grape, T., Hammarström, A., Hogstedt, C., Marteinsdottir, I., Skoog, I., Träskman-Bendz, L., Hall, C., 2017. A systematic review including meta-

analysis of work environment and burnout symptoms. BMC Public Health 17 (1), 264.
Balog, P., Falger, P.R.J., Szabó, G., Rafael, B., Székely, A., Konkolÿ Thege, B., 2017. Are vital exhaustion and depression independent risk factors for cardiovascular disease morbidity? Health Psychol. 36 (8), 740–748.
Beardslee, W.R., Versage, E.M., Gladstone, T.R., 1998. Children of affectively ill parents: a review of the past 10 years. J. Am. Acad. Child Adolesc. Psychiatry 37 (11), 1134–1141.
Bellingrath, S., Weigl, T., Kudielka, B.M., 2008. Cortisol dysregulation in school teachers in relation to burnout, vital exhaustion, and effort-reward-imbalance. Biol. Psychol. 78 (1), 104–113.
Chumaeva, N., Hintsanen, M., Pulkki-Råback, L., Jokela, M., Juonala, M., Lehtimäki, T., Raitakari, O.T., Keltikangas-Järvinen, L., 2014. Interleukin-6 gene polymorphism, chronic stress and atherosclerosis: interleukin-6-174G>C polymorphism, chronic stress and risk of early atherosclerosis in the Cardiovascular Risk in Young Finns Study. J. Psychosom. Res. 76 (4), 333–338.
Consortium, S.W.G.o.t.P.G., 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511 (7510), 421–427.
Das, S., Forer, L., Schönherr, S., Sidore, C., Locke, A.E., Kwong, A., Vrieze, S.I., Chew, E. Y., Levy, S., McGue, M., Schlessinger, D., Stambolian, D., Loh, P.R., Iacono, W.G., Swaroop, A., Scott, L.J., Cucca, F., Kronenberg, F., Boehnke, M., Abecasis, G.R., Fuchsberger, C., 2016. Next-generation genotype imputation service and methods. Nat. Genet. 48 (10), 1284–1287.
Elo, A.L., Leppänen, A., Lindström, K., Ropponen, T., 1992. OSQ: occupational stress Questionnaire: user's Instructions. Institute of Occupational Health, Publication Office.
Engen, M.J., Lyngstad, S.H., Ueland, T., Simonsen, C.E., Vaskinn, A., Smeland, O., Bettella, F., Lagerberg, T.V., Djurovic, S., Andreassen, O.A., Melle, I., 2020. Polygenic scores for schizophrenia and general cognitive ability: associations with six cognitive domains, premorbid intelligence, and cognitive composite score in individuals with a psychotic disorder and in healthy controls. Transl Psychiatry 10 (1), 416.
Evensen, S., Wisløff, T., Lystad, J.U., Bull, H., Ueland, T., Falkum, E., 2016. Prevalence, Employment Rate, and Cost of Schizophrenia in a High-Income Welfare Society: a Population-Based Study Using Comprehensive Health and Welfare Registers. Schizophr. Bull. 42 (2), 476–483.
Fanelli, G., Benedetti, F., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., Forloni, G., Ferentinos, P., Rujescu, D., Mendlewicz, J., Serretti, A., Fabbri, C., 2021. Higher polygenic risk scores for schizophrenia may be suggestive of treatment non-response in major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 108, 110170.
Gottesman, I.I., Laursen, T.M., Bertelsen, A., Mortensen, P.B., 2010. Severe mental disorders in offspring with 2 psychiatrically ill parents. Arch. Gen. Psychiatry 67 (3), 252–257.
Hatzimanolis, A., Avramopoulos, D., Arking, D.E., Moes, A., Bhatnagar, P., Lencz, T., Malhotra, A.K., Giakoumaki, S.G., Roussos, P., Smyrnis, N., Bitsios, P., Stefanis, N.C., 2018. Stress-Dependent Association Between Polygenic Risk for Schizophrenia and Schizotypal Traits in Young Army Recruits. Schizophr. Bull. 44 (2), 338–347.
Hintsanen, M., Elovainio, M., Puttonen, S., Kivimäki, M., Lehtimäki, T., Kähönen, M., Juonala, M., Rontu, R., Viikari, J.S., Raitakari, O.T., Keltikangas-Järvinen, L., 2008. Val/Met polymorphism of the COMT gene moderates the association between job strain and early atherosclerosis in young men. J. Occup. Environ. Med. 50 (6), 649–657.
Hintsanen, M., Elovainio, M., Puttonen, S., Kivimäki, M., Raitakari, O.T., Lehtimäki, T., Rontu, R., Juonala, M., Kähönen, M., Viikari, J., Keltikangas-Järvinen, L., 2007. Neuregulin-1 genotype moderates the association between job strain and early atherosclerosis in young men. Ann. Behav. Med. 33 (2), 148–155.
Howard, D.M., Adams, M.J., Clarke, T.K., Hafferty, J.D., Gibson, J., Shirali, M., Coleman, J.R.I., Hagenaars, S.P., Ward, J., Wigmore, E.M., Alloza, C., Shen, X., Barbu, M.C., Xu, E.Y., Whalley, H.C., Marioni, R.E., Porteous, D.J., Davies, G., Deary, I.J., Hemani, G., Berger, K., Teismann, H., Rawal, R., Arolt, V., Baune, B.T., Dannlowski, U., Domschke, K., Tian, C., Hinds, D.A., Trzaskowski, M., Byrne, E.M., Ripke, S., Smith, D.J., Sullivan, P.F., Wray, N.R., Breen, G., Lewis, C.M., McIntosh, A. M., 2019. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat. Neurosci. 22 (3), 343–352.
Howard, D.M., Adams, M.J., Shirali, M., Clarke, T.K., Marioni, R.E., Davies, G., Coleman, J.R.I., Alloza, C., Shen, X., Barbu, M.C., Wigmore, E.M., Gibson, J., Hagenaars, S.P., Lewis, C.M., Ward, J., Smith, D.J., Sullivan, P.F., Haley, C.S., Breen, G., Deary, I.J., McIntosh, A.M., 2018. Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. Nat. Commun. 9 (1), 1470.
Igo Jr., R.P., Kinzy, T.G., Cooke Bailey, J.N., 2019. Genetic Risk Scores. Curr. Protoc. Hum. Genet. 104 (1), e95.
II, G., 1991. Schizophrenia genesis: the Origin of Madness. Freeman, New York.
Janszky, I., Lekander, M., Blom, M., Georgiades, A., Ahnve, S., 2005. Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease. Brain Behav. Immun. 19 (6), 555–563.
Karasek, R.A., 1985. Job content questionnaire. J. Occup. Health Psychol.
Keltikangas-Järvinen, L., Heponiemi, T., 2004. Vital exhaustion, temperament, and cardiac reactivity in task-induced stress. Biol. Psychol. 65 (2), 121–135.
Ketvel, L., Keltikangas-Järvinen, L., Pahkala, K., Juonala, M., Ahola-Olli, A., Lehtimäki, T., Viikari, J., Raitakari, O., Rovio, S., Saarinen, A., 2023. Stress-Related Exhaustion, Polygenic Cognitive Potential, and Cognitive Test Performance - A General Population Study. Cognit Ther Res 47 (2), 155–167.
Kiviniemi, M., Suvisaari, J., Pirkola, S., Läksy, K., Häkkinen, U., Isohanni, M., Hakko, H., 2011. Five-year follow-up study of disability pension rates in first-onset schizophrenia with special focus on regional differences and mortality. Gen. Hosp. Psychiatry 33 (5), 509–517.
Kop, W.J., Hamulyák, K., Pernot, C., Appels, A., 1998. Relationship of blood coagulation and fibrinolysis to vital exhaustion. Psychosom. Med. 60 (3), 352–358.
Kudielka, B.M., von Kanel, R., Gander, M.L., Fischer, J.E., 2004. The interrelationship of psychosocial risk factors for coronary artery disease in a working population: do we measure distinct or overlapping psychological concepts? Behav. Med. 30 (1), 35–43.
Kudielka, B.M., von Känel, R., Preckel, D., Zgraggen, L., Mischler, K., Fischer, J.E., 2006. Exhaustion is associated with reduced habituation of free cortisol responses to repeated acute psychosocial stress. Biol. Psychol. 72 (2), 147–153.
Kulikowski, K., 2021. Cognitive abilities-a new direction in burnout research. Eur. J. Work Organ. Psychol. 30 (5), 705–719.
Landsbergis, P.A., Schnall, P.L., Warren, K., Pickering, T.G., Schwartz, J.E., 1994. Association between ambulatory blood pressure and alternative formulations of job strain. Scand. J. Work Environ. Health 20 (5), 349–363.
Lauronen, E., Miettunen, J., Veijola, J., Karhu, M., Jones, P.B., Isohanni, M., 2007. Outcome and its predictors in schizophrenia within the Northern Finland 1966 Birth Cohort. Eur. Psychiatry 22 (2), 129–136.
Legge, S.E., Santoro, M.L., Periyasamy, S., Okewole, A., Arsalan, A., Kowalec, K., 2021. Genetic architecture of schizophrenia: a review of major advancements. Psychol. Med. 51 (13), 2168–2177.
Lerman, Y., Melamed, S., Shragin, Y., Kushnir, T., Rotgoltz, Y., Shirom, A., Aronson, M., 1999. Association between burnout at work and leukocyte adhesiveness/aggregation. Psychosom. Med. 61 (6), 828–833.
Lerner, D., Adler, D.A., Chang, H., Lapitsky, L., Hood, M.Y., Perissinotto, C., Reed, J., McLaughlin, T.J., Berndt, E.R., Rogers, W.H., 2004. Unemployment, job retention, and productivity loss among employees with depression. Psychiatr. Serv. 55 (12), 1371–1378.
MacCallum, R.C., Zhang, S., Preacher, K.J., Rucker, D.D., 2002. On the practice of dichotomization of quantitative variables. Psychol. Methods 7 (1), 19–40.
Maslach, C., Leiter, M.P., 2021. How to Measure Burnout Accurately and Ethically. Harv. Bus. Rev.
Mistry, S., Harrison, J.R., Smith, D.J., Escott-Price, V., Zammit, S., 2018. The use of polygenic risk scores to identify phenotypes associated with genetic risk of bipolar disorder and depression: a systematic review. J. Affect. Disord. 234, 148–155.
Murray, G.K., Lin, T., Austin, J., McGrath, J.J., Hickie, I.B., Wray, N.R., 2021. Could Polygenic Risk Scores Be Useful in Psychiatry?: a Review. JAMA Psychiatry 78 (2), 210–219.
Musliner, K.L., Mortensen, P.B., McGrath, J.J., Suppli, N.P., Hougaard, D.M., Bybjerg-Grauholm, J., Bækvad-Hansen, M., Andreassen, O., Pedersen, C.B., Pedersen, M.G., Mors, O., Nordentoft, M., Børglum, A.D., Werge, T., Agerbo, E., 2019. Association of Polygenic Liabilities for Major Depression, Bipolar Disorder, and Schizophrenia With Risk for Depression in the Danish Population. JAMA Psychiatry 76 (5), 516–525.
Naczenski, L.M., Vries, J.D., Hooff, M., Kompier, M.A.J., 2017. Systematic review of the association between physical activity and burnout. J. Occup. Health 59 (6), 477–494.
Nicolson, N.A., van Diest, R., 2000. Salivary cortisol patterns in vital exhaustion. J. Psychosom. Res. 49 (5), 335–342.
Plieger, T., Melchers, M., Felten, A., Lieser, T., Meermann, R., Reuter, M., 2019. Moderator Effects of Life Stress on the Association between MAOA-uVNTR, Depression, and Burnout. Neuropsychobiology 78 (2), 86–94.
Power, R.A., Steinberg, S., Bjornsdottir, G., Rietveld, C.A., Abdellaoui, A., Nivard, M.M., Johannesson, M., Galesloot, T.E., Hottenga, J.J., Willemsen, G., Cesarini, D., Benjamin, D.J., Magnusson, P.K., Ullén, F., Tiemeier, H., Hofman, A., van Rooij, F.J., Walters, G.B., Sigurdsson, E., Thorgeirsson, T.E., Ingason, A., Helgason, A., Kong, A., Kiemeney, L.A., Koellinger, P., Boomsma, D.I., Gudbjartsson, D., Stefansson, H., Stefansson, K., 2015. Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. Nat. Neurosci. 18 (7), 953–955.
Preckel, D., von Känel, R., Kudielka, B.M., Fischer, J.E., 2005. Overcommitment to work is associated with vital exhaustion. Int. Arch. Occup. Environ. Health 78 (2), 117–122.
Pulkki-Råback, L., Elovainio, M., Hakulinen, C., Lipsanen, J., Hintsanen, M., Jokela, M., Kubzansky, L.D., Hintsa, T., Serlachius, A., Laitinen, T.T., Pahkala, K., Mikkilä, V., Nevalainen, J., Hutri-Kähönen, N., Juonala, M., Viikari, J., Raitakari, O.T., Keltikangas-Järvinen, L., 2015. Cumulative effect of psychosocial factors in youth on ideal cardiovascular health in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation 131 (3), 245–253.
Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A., Bender, D., Maller, J., Sklar, P., de Bakker, P.I., Daly, M.J., Sham, P.C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. 81 (3), 559–575.
Raitakari, O.T., Juonala, M., Rönnemaa, T., Keltikangas-Järvinen, L., Räsänen, L., Pietikäinen, M., Hutri-Kähönen, N., Taittonen, L., Jokinen, E., Marniemi, J., Jula, A., Telama, R., Kähönen, M., Lehtimäki, T., Akerblom, H.K., Viikari, J.S., 2008. Cohort profile: the cardiovascular risk in Young Finns Study. Int. J. Epidemiol. 37 (6), 1220–1226.
Richards, A., Horwood, J., Boden, J., Kennedy, M., Sellers, R., Riglin, L., Mistry, S., Jones, H., Smith, D.J., Zammit, S., Owen, M., O'Donovan, M.C., Harold, G.T., 2019. Associations between schizophrenia genetic risk, anxiety disorders and manic/hypomanic episode in a longitudinal population cohort study. Br. J. Psychiatry 214 (2), 96–102.
Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J.L., Kähler, A.K., Akterin, S., Bergen, S. E., Collins, A.L., Crowley, J.J., Fromer, M., Kim, Y., Lee, S.H., Magnusson, P.K., Sanchez, N., Stahl, E.A., Williams, S., Wray, N.R., Xia, K., Bettella, F., Borglum, A.D.,

Bulik-Sullivan, B.K., Cormican, P., Craddock, N., de Leeuw, C., Durmishi, N., Gill, M., Golimbet, V., Hamshere, M.L., Holmans, P., Hougaard, D.M., Kendler, K.S., Lin, K., Morris, D.W., Mors, O., Mortensen, P.B., Neale, B.M., O'Neill, F.A., Owen, M.J., Milovancevic, M.P., Posthuma, D., Powell, J., Richards, A.L., Riley, B.P., Ruderfer, D., Rujescu, D., Sigurdsson, E., Silagadze, T., Smit, A.B., Stefansson, H., Steinberg, S., Suvisaari, J., Tosato, S., Verhage, M., Walters, J.T., Levinson, D.F., Gejman, P.V., Kendler, K.S., Laurent, C., Mowry, B.J., O'Donovan, M.C., Owen, M.J., Pulver, A.E., Riley, B.P., Schwab, S.G., Wildenauer, D.B., Dudbridge, F., Holmans, P., Shi, J., Albus, M., Alexander, M., Campion, D., Cohen, D., Dikeos, D., Duan, J., Eichhammer, P., Godard, S., Hansen, M., Lerer, F.B., Liang, K.Y., Maier, W., Mallet, J., Nertney, D.A., Nestadt, G., Norton, N., O'Neill, F.A., Papadimitriou, G.N., Ribble, R., Sanders, A.R., Silverman, J.M., Walsh, D., Williams, N.M., Wormley, B., Arranz, M.J., Bakker, S., Bender, S., Bramon, E., Collier, D., Crespo-Facorro, B., Hall, J., Iyegbe, C., Jablensky, A., Kahn, R.S., Kalaydjieva, L., Lawrie, S., Lewis, C.M., Lin, K., Linszen, D.H., Mata, I., McIntosh, A., Murray, R.M., Ophoff, R.A., Powell, J., Rujescu, D., Van Os, J., Walshe, M., Weisbrod, M., Wiersma, D., Donnelly, P., Barroso, I., Blackwell, J.M., Bramon, E., Brown, M.A., Casas, J.P., Corvin, A.P., Deloukas, P., Duncanson, A., Jankowski, J., Markus, H.S., Mathew, C.G., Palmer, C. N., Plomin, R., Rautanen, A., Sawcer, S.J., Trembath, R.C., Viswanathan, A.C., Wood, N.W., Spencer, C.C., Band, G., Bellenguez, C., Freeman, C., Hellenthal, G., Giannoulatou, E., Pirinen, M., Pearson, R.D., Strange, A., Su, Z., Vukcevic, D., Donnelly, P., Langford, C., Hunt, S.E., Edkins, S., Gwilliam, R., Blackburn, H., Bumpstead, S.J., Dronov, S., Gillman, M., Gray, E., Hammond, N., Jayakumar, A., McCann, O.T., Liddle, J., Potter, S.C., Ravindrarajah, R., Ricketts, M., Tashakkori-Ghanbaria, A., Waller, M.J., Weston, P., Widaa, S., Whittaker, P., Barroso, I., Deloukas, P., Mathew, C.G., Blackwell, J.M., Brown, M.A., Corvin, A.P., McCarthy, M.I., Spencer, C.C., Bramon, E., Corvin, A.P., O'Donovan, M.C., Stefansson, K., Scolnick, E., Purcell, S., McCarroll, S.A., Sklar, P., Hultman, C.M., Sullivan, P.F., 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat. Genet. 45 (10), 1150–1159.

Ruotsalainen, J.H., Verbeek, J.H., Mariné, A., Serra, C., 2015. Preventing occupational stress in healthcare workers. Cochrane Database Syst. Rev. 2015 (4), Cd002892.

Saarinen, A., Lyytikäinen, L.P., Hietala, J., Dobewall, H., Lavonius, V., Raitakari, O., Kähönen, M., Sormunen, E., Lehtimäki, T., Keltikangas-Järvinen, L., 2022. Magical thinking in individuals with high polygenic risk for schizophrenia but no non-affective psychoses-a general population study. Mol. Psychiatry.

Saiepour, N., Najman, J.M., Ware, R., Baker, P., Clavarino, A.M., Williams, G.M., 2019. Does attrition affect estimates of association: a longitudinal study. J. Psychiatr. Res. 110, 127–142.

Schmitt, S., Meller, T., Stein, F., Brosch, K., Ringwald, K., Pfarr, J.K., Bordin, C., Peusch, N., Steinsträter, O., Grotegerd, D., Dohm, K., Meinert, S., Förster, K., Redlich, R., Opel, N., Hahn, T., Jansen, A., Forstner, A.J., Streit, F., Witt, S.H., Rietschel, M., Müller-Myhsok, B., Nöthen, M.M., Dannlowski, U., Krug, A., Kircher, T., Nenadić, I., 2021. Effects of polygenic risk for major mental disorders and cross-disorder on cortical complexity. Psychol. Med. 1–12.

Schnorpfeil, P., Noll, A., Wirtz, P., Schulze, R., Ehlert, U., Frey, K., Fischer, J.E., 2002. Assessment of exhaustion and related risk factors in employees in the manufacturing industry–a cross-sectional study. Int. Arch. Occup. Environ. Health 75 (8), 535–540.

Schubert, K.O., Thalamuthu, A., Amare, A.T., Frank, J., Streit, F., Adl, M., Akula, N., Akiyama, K., Ardau, R., Arias, B., Aubry, J.M., Backlund, L., Bhattacharjee, A.K., Bellivier, F., Benabarre, A., Bengesser, S., Biernacka, J.M., Birner, A., Marie-Claire, C., Cearns, M., Cervantes, P., Chen, H.C., Chillotti, C., Cichon, S., Clark, S.R., Cruceanu, C., Czerski, P.M., Dalkner, N., Dayer, A., Degenhardt, F., Del Zompo, M., DePaulo, J.R., Étain, B., Falkai, P., Forstner, A.J., Frisen, L., Frye, M.A., Fullerton, J. M., Gard, S., Garnham, J.S., Goes, F.S., Grigoroiu-Serbanescu, M., Grof, P., Hashimoto, R., Hauser, J., Heilbronner, U., Herms, S., Hoffmann, P., Hou, L., Hsu, Y. H., Jamain, S., Jiménez, E., Kahn, J.P., Kassem, L., Kuo, P.H., Kato, T., Kelsoe, J., Kittel-Schneider, S., Ferensztajn-Rochowiak, E., König, B., Kusumi, I., Laje, G., Landén, M., Lavebratt, C., Leboyer, M., Leckband, S.G., Maj, M., Manchia, M., Martinsson, L., McCarthy, M.J., McElroy, S., Colom, F., Mitjans, M., Mondimore, F. M., Monteleone, P., Nievergelt, C.M., Nöthen, M.M., Novák, T., O'Donovan, C., Ozaki, N., Ösby, U., Papiol, S., Pfennig, A., Pisanu, C., Potash, J.B., Reif, A., Reininghaus, E., Rouleau, G.A., Rybakowski, J.K., Schalling, M., Schofield, P.R., Schweizer, B.W., Severino, G., Shekhtman, T., Shilling, P.D., Shimoda, K., Simhandl, C., Slaney, C.M., Squassina, A., Stamm, T., Stopkova, P., Tekola-Ayele, F., Tortorella, A., Turecki, G., Veeh, J., Vieta, E., Witt, S.H., Roberts, G., Zandi, P.P., Alda, M., Bauer, M., McMahon, F.J., Mitchell, P.B., Schulze, T.G., Rietschel, M., Baune, B.T., 2021. Combining schizophrenia and depression polygenic risk scores improves the genetic prediction of lithium response in bipolar disorder patients. Transl. Psychiatry 11 (1), 606.

Sorensen, H.J., Debost, J.C., Agerbo, E., Benros, M.E., McGrath, J.J., Mortensen, P.B., Ranning, A., Hjorthoj, C., Mors, O., Nordentoft, M., Petersen, L., 2018. Polygenic Risk Scores, School Achievement, and Risk for Schizophrenia: a Danish Population-Based Study. Biol. Psychiatry 84 (9), 684–691.

Sormunen, E., Saarinen, M.M., Salokangas, R.K.R., Telama, R., Hutri-Kähönen, N., Tammelin, T., Viikari, J., Raitakari, O., Hietala, J., 2017. Effects of childhood and adolescence physical activity patterns on psychosis risk-a general population cohort study. NPJ Schizophr 3, 5.

Suls, J., Bunde, J., 2005. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. Psychol. Bull. 131 (2), 260–300.

Sund, R., 2012. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand. J. Public Health 40 (6), 505–515.

Suvisaari, J.M., Haukka, J.K., Tanskanen, A.J., Lönnqvist, J.K., 1999. Decline in the incidence of schizophrenia in Finnish cohorts born from 1954 to 1965. Arch. Gen. Psychiatry 56 (8), 733–740.

van Diest, R., Appels, A., 1991. Vital exhaustion and depression: a conceptual study. J. Psychosom. Res. 35 (4–5), 535–544.

Viinikainen, J., Böckerman, P., Hakulinen, C., Kari, J.T., Lehtimäki, T., Raitakari, O., Pehkonen, J., 2022. Schizophrenia polygenic risk score and long-term success in the labour market: a cohort study. J. Psychiatr. Res.

Vroege, E.M., Zuidersma, M., de Jonge, P., 2012. Vital exhaustion and somatic depression: the same underlying construct in patients with myocardial infarction? Psychosom. Med. 74 (5), 446–451.

Wang, S.H., Lai, R.Y., Lee, Y.C., Su, M.H., Chen, C.Y., Hsiao, P.C., Yang, A.C., Liu, Y.L., Tsai, S.J., Kuo, P.H., 2020. Association between polygenic liability for schizophrenia and substance involvement: a nationwide population-based study in Taiwan. Genes Brain Behav. 19 (5), e12639.

Yi, X., Li, X., Ma, X., Li, F., 2022. The relationship between occupational stress and job burnout in coal miners: interactions between GCCR and SLC6A4 gene polymorphisms and the environment. J. Affect. Disord. 297, 76–82.