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Associations between lifestyle, genetic liability for severe mental illness and risk of incident somatic illnesses

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People with severe mental illness (SMI), including schizophrenia (SCZ) and bipolar disorder (BD), show elevated risk for somatic conditions and premature mortality. Both genetic liability and modifiable lifestyle factors have been implicated in this comorbidity, yet large-scale studies examining their independent and combined effects across multiple somatic conditions are lacking. We therefore examined whether modifiable lifestyle factors (i.e. smoking, alcohol intake, diet, and exercise) and polygenic risk scores (PRS) for SCZ and BD are associated with the risk of developing somatic illnesses. Data were drawn from 315,313 unrelated individuals in the UK Biobank cohort, with a median follow up of 14 years. Cox proportional hazards models were used to estimate the independent, joint, and interaction effects of PRS-SCZ and PRS-BD and lifestyle factors on the incidence of nine chronic somatic illnesses. Healthy lifestyle was associated with lower risks of type 2 diabetes (T2D), cardiovascular disease (CVD), dementia, rheumatoid arthritis, asthma, chronic liver disease (CLD), and cancer (HRs ranging from 0.43 to 0.80). In addition, higher PRS for SCZ was associated with increased risks of asthma and dementia and lower risk of T2D, while higher PRS for BD was associated with increased risk of T2D. Moreover, likelihood ratio tests confirmed that PRS-SCZ and PRS-BD each contribute independent information to the joint Cox model for T2D, indicating that the opposing directions of their associations with T2D risk are not driven by shared genetic variance between the two scores. Finally, individuals with a healthy lifestyle consistently showed lower risks of CLD, T2D, CVD, and dementia across genetic risk strata; however, no significant additive interaction was observed between genetic risk and lifestyle factors. In conclusion, these findings indicate that genetic liabilities for SCZ and BD show outcome-specific associations with somatic illnesses, while a healthy lifestyle is associated with lower somatic illness risk regardless of genetic risk level.

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INTRODUCTION

The comorbidity between severe mental illnesses (SMI) and somatic disorders is well established [1–3]. However, despite strong epidemiological evidence linking mental and somatic illnesses, the underlying factors remain largely unexplained. This relationship appears to be bidirectional: the presence of SMI increases the risk for physical disorders, while chronic somatic conditions can, in turn, elevate the likelihood of developing or exacerbating psychiatric conditions [4–6]. SMI may affect socio-economic status, daily functioning, and lifestyle habits of the individuals, which can mediate or moderate the risk of developing somatic illness [7]. Additionally, people living with psychiatric disorders often face disparities in healthcare access, hindering timely diagnosis and treatment for physical conditions [8].

Evidence from longitudinal studies suggests a temporal sequence where the onset of a mental disorder often precedes later development of medical conditions [9–11]. People with SMI, such as bipolar disorders (BD) and schizophrenia (SCZ), experience higher rates of comorbid medical conditions and lower life expectancy compared to the general population [12–14]. Moreover, the odds of physical multimorbidity in individuals with SMI are nearly double that of people without SMI [15]. These patterns of comorbidities may complicate the clinical course of SMI and worsen prognosis, partly due to higher mortality rates, which are largely determined by cardiovascular, infectious, and metabolic conditions [1]. The disparity in health outcomes between patients with and without SMI represents a major public health concern, with evidence indicating that the mortality gap driven by physical illnesses in people living with SMI is on the rise [3, 16]. While much

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of this evidence derives from studies of clinically diagnosed SMI, genetic liability for these disorders is distributed across the general population, and individuals without a clinical diagnosis may still carry elevated genetic risk that influences somatic health outcomes.

Genetic factors are hypothesized to contribute significantly to the overall pathogenesis of SMI and to partly explain the comorbidity between SMI and somatic conditions [17–23]. Large-scale genome-wide association studies (GWAS) have demonstrated that SMIs are highly polygenic, involving many genetic variants, most of which have small individual effects [24–26]. A polygenic risk score (PRS), a single per-individual score, is calculated on the weighted sum of the number of risk alleles and measures the individual genetic predisposition for developing a certain trait or disease. PRS can be used as a proxy for disease risk, offering a powerful approach to investigate the associations between SMIs and somatic illnesses. Therefore, adding PRS to existing disease risk prediction models provides insight into the relative contribution of genetic and non-genetic factors, offering a clearer understanding of individual risk profiles [27].

Previous research has shown that modifiable health behaviors are associated with a wide range of adverse health outcomes, including increased risks for somatic conditions and premature mortality [28, 29]. Adhering to healthy lifestyle (healthy diet, regular physical activity, and avoidance of smoking and of excessive alcohol consumption) reduces risks of developing several chronic conditions, such as cardiovascular disease (CVD) [30], type 2 diabetes (T2D) [31], dementia [32], cancer [33], and others. Beyond reducing risk, healthy lifestyle may also attenuate disease severity and progression through interrelated biological mechanisms, including modulation of chronic low-grade inflammation, improved metabolic regulation, and enhanced immune function [34–36]. Since these lifestyle behaviors are largely modifiable, understanding their relative contributions to somatic illness risk may help guide effective prevention strategies.

Although advances have been made in understanding the links between SMI and somatic diseases, knowledge about the scope and magnitude of these associations remains limited. Studying the associations between psychiatric disorders and somatic conditions can be challenging due to various reasons, i.e., diagnostic complexity of these disorders [37], treatment-related confounding [38], and the relatively low prevalence of certain psychiatric conditions in certain cohorts [39, 40]. As a result, most of the existing evidence focuses on studying the links between specific illness dyads and is often derived from small-scale, cross-sectional studies. We therefore set out to investigate the extent to which modifiable lifestyle factors and genetic risk for SCZ and BD are associated with risks of incident somatic illnesses. To assess the possible risk reduction associated with healthy lifestyle factors, we first examined whether a healthier lifestyle profile, assessed at baseline, was linked to lower risks of developing somatic illnesses. To evaluate the independent contributions of genetic liability for SMI, we then investigated whether PRS for SCZ and BD were associated with incidences of somatic illnesses. Finally, we explored the joint effects and potential interactions between genetic risks and lifestyle factors in relation to somatic illness risk, aiming to examine whether lifestyle factors and genetic risk show independent or combined associations with somatic illness incidence.

METHODS AND MATERIALS

Study population

For this observational study, we used data from the UK Biobank (UKB) cohort, a large population-based prospective study that recruited over 500,000 individuals aged 40–69 between 2006 and 2010 [41]. Details of the study protocol have been published elsewhere [42]. Baseline data were

collected at 22 assessment centers across the United Kingdom via questionnaires, verbal interviews, physical examinations, and biological samples, while follow-up information was gathered via linkage to electronic medical records, including death and cancer registries and hospital inpatient records. The study received ethical approval from the North West Multi-center Research Ethics Committee (REC reference 11/NW/03820). All participants provided written informed consent before enrolment to the study.

To minimize the risk of population stratification incurring bias in the statistical analyses, we restricted our sample to 315,313 participants of White-British ancestry (Data-Field 21000). As standard genetic quality control measures, we excluded individuals with outliers for heterozygosity or missing genotype rates (Data-Field 22027); with sex chromosome aneuploidy (Data-Field 22019); with mismatched reported and genetic sex (Data-Fields 31 and 22001); and/or with close genetic kinship (Data-Field 22021) [41]. Participants with close genetic kinship were identified using the KING kinship estimator with a threshold of >0.0442, corresponding to third-degree relatives or closer. To focus exclusively on incident cases of each somatic illness, we further refined our analysis by excluding participants with pre-existing diagnoses of the respective conditions in each statistical model (see Figure S1 in Supplementary Material). No exclusions were made based on psychiatric diagnoses to preserve the full spectrum of genetic liability. Individuals with missing data on any outcome, exposure, or covariate were excluded from each model; complete-case analysis was used as the primary analytical approach. The present analyses were conducted under UK Biobank application number 54176.

Exposures

Polygenic risk scores. To evaluate the associations between genetic risk for SMIs and the incidence of somatic illnesses, we leveraged the standard PRS for SCZ and BD provided by the UK Biobank PRS Release [43]. The Standard PRS set was calculated for all individuals in the UKB, using a proprietary algorithm developed by Genomics plc [43], trained exclusively on external GWAS data with no UK Biobank overlap, and has been shown to outperform a broad range of published PRSs [44]. Specifically, the SCZ PRS was based on the GWAS by Trubetskoy et al. (2022) [26] and the BD PRS on the GWAS by Mullins et al. (2021) [25]. For ease of interpretation and visualization (not in our analyses), we classified PRS as low risk (lowest quintile), intermediate risk (quintiles 2 to 4) and high risk (highest quintile), as per previous studies [45, 46].

Healthy lifestyle factors. To examine associations between lifestyle factors and the incidence of somatic illnesses, a composite lifestyle score reflecting smoking status, alcohol consumption, physical activity, and diet was constructed following the approach of Lourida et al (2019) [45]. These modifiable lifestyle habits have been previously identified as key factors for improving physical health in individuals with mental illness [3]. Here, the standardized lifestyle score was categorized into “healthy” (3 or 4 healthy lifestyle factors), “moderately healthy” (2 healthy lifestyle factors), and “unhealthy” (0 or 1 healthy lifestyle factor) groups [45, 47]. The detailed description of the calculation of the composite lifestyle scores is provided in Table S1. We also examined associations of individual lifestyle factors with the incidences of somatic illnesses, to capture the possible influence of each lifestyle component on disease risk.

Outcomes. The outcome of interest for each model was the incidence of the somatic illness during follow-up. For this analysis, we selected the somatic illnesses carrying the highest prevalence in psychiatric disorders and those associated with the highest mortality, i.e. asthma [48], CVD [49], autoimmune disorders including rheumatoid arthritis and inflammatory bowel disease (IBD) [50], T2D [51], dementia [10], cancer [52], Parkinson’s disease [23], and chronic liver disease (CLD) [53]. In each disease-specific analysis, we excluded prevalent cases of the respective illness to focus solely on incident cases. Participants were classified as having prevalent cases of somatic illnesses if they had a hospital-recorded diagnosis prior to baseline or self-reported the illness at baseline. Self-reported cases identified post-baseline without supporting hospital records were also excluded to minimize the risk of follow-up bias. All primary outcomes, defined as incident somatic illnesses classified according to the 10th revision of the International Statistical Classification of Disease (ICD-10), along with their corresponding ICD-10 codes and self-reported UKB field codes, are listed in Table S2. A flowchart outlining the sample selection process is provided in Figure S1.

Follow-up time was calculated as the time from the baseline assessment date to the earliest of the following: the date of the first recorded incident event (i.e. the somatic illness recorded), the date of death, or the censoring date of hospital inpatient records, whichever came first. Censoring dates varied by region, corresponding to the last available follow-up: October 31, 2022, for England; August 31, 2022, for Scotland; and May 31, 2022, for Wales. For participants with no recorded event or death, follow-up was censored at the regional last follow-up date.

Statistical analysis

Multivariate Cox proportional hazards models were applied to examine associations of genetic and lifestyle factors and the incidence of each somatic illness individually. The models were fitted to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the events of interest, i.e., the incidence of somatic illnesses, with competing risks treated as censoring events. The covariates for this study were selected based on prior research [27, 54, 55] and availability at baseline: all models incorporated follow-up time as the time-to-event component and were adjusted for key covariates, i.e., age (Data-Field 21022), sex (Data-Field 31), education (Data-Field 6138), and employment (Data-Field 6141), all retrieved from the UKB baseline questionnaires. BMI was not included as a covariate as it is likely to act as a mediator on the causal pathway between lifestyle behaviours and somatic illness outcomes, and adjusting for it could introduce overadjustment bias [56]. For the models including PRS (as independent variables), we additionally adjusted for the first 10 genetic ancestry principal components (Data-Field 22009) to correct for population stratification [47, 57]. To evaluate the joint effects of genetic risk and lifestyle factors, interaction terms were included in the models, and stratified analyses were conducted to explore the differential impact of these factors across subgroups, i.e., PRS and lifestyle categories. The additive interaction analysis was conducted to determine whether the combined effect of lifestyle and PRS exceeded the sum of their individual effects. This was assessed using the relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP), providing insights into potential synergistic or antagonistic effects. For this analysis, we compared the most extreme exposure groups: participants with low PRS and a healthy lifestyle versus those with high PRS and an unhealthy lifestyle, the latter serving as the reference category (HR = 1.0). To assess possible multiplicative interaction between genetic risks and lifestyle factors, we included an interaction term in the regression models (genetic risk × lifestyle factor) and tested whether the combined effect of these exposures on disease risk deviated from the product of their individual effects. The interaction categories included high, intermediate, and low PRS groups, each stratified by healthy, moderately healthy, and unhealthy lifestyles, with high PRS & unhealthy lifestyle as the reference category (HR = 1.0).

We conducted sensitivity analyses to assess the robustness of our results. Prior to analysis, the dataset was examined for missing values across key predictors and covariates to assess the extent and patterns of missingness. The proportion of missing data was reviewed to ensure that it did not systematically affect specific subgroups or variables critical to the analysis. Participants who selected “do not know” or “prefer not to answer” options when filling out the questionnaires were recoded as missing or null. Missing data were below 1% for predictors and covariates, except for lifestyle scores, which exhibited 59% missingness across datasets for somatic illnesses. To address potential biases, our first sensitivity analysis was conducted on the imputed datasets for lifestyle models, generated through multiple imputations using the chained equations (MICE) technique [58]. Multiple imputation produces less biased estimates and lower root mean square errors compared to other imputation techniques, even at high levels of missing data ranging from 10% to 80% [59]. However, while multiple imputation under the missing at random (MAR) assumption produces less biased estimates than complete-case analysis in many scenarios, its superiority cannot be assumed a priori and depends on the underlying missing data mechanism [60]. We generated 60 imputed datasets, a number chosen to be at least equal to the percentage of missing data (59%), in line with current recommendations [61]. Cox proportional hazards models were fitted separately within each imputed dataset, and regression coefficients and standard errors were combined using Rubin’s rules to obtain pooled hazard ratios and confidence intervals. The second sensitivity analysis was conducted using a continuous total lifestyle score instead of composite lifestyle score, calculated as the sum of individual healthy lifestyle factors, ranging from 0 (least healthy) to 4 (most healthy). A third sensitivity analysis was conducted using a reclassified employment variable distinguishing retired individuals from unemployed individuals, given that retirement represents a voluntary transition distinct from involuntary unemployment. A fourth sensitivity analysis excluded

Table 1. Baseline Sociodemographic and Clinical Characteristics of the Study Population (N = 315,313).

Characteristic	Category	N (%)
Sex	Female	169,335 (53.7)
	Male	145,978 (46.3)
Age, mean (SD)		56.66
Education	Higher	108,086 (34.6)
	Lower Secondary	81,878 (26.2)
	Upper Secondary	36,885 (11.8)
	Vocational	19,640 (6.3)
	Other	65,773 (21.1)
Employment	Employed	183,696 (58.4)
	Unemployed	120,073 (41.1)
	Other	1,569 (0.5)
Lifestyle Score	Healthy	77,284 (60.1)
	Moderately Healthy	36,859 (28.7)
	Unhealthy	14,366 (11.2)
PRS-SCZ	Low	62,999 (20.0)
	Intermediate	188,993 (60.0)
	High	63,000 (20.0)
PRS-BD	Low	62,999 (20.0)
	Intermediate	188,994 (60.0)
	High	62,999 (20.0)

SCZ schizophrenia, BD bipolar disorder, PRS polygenic risk score.

Lifestyle score categories are based on a composite of smoking, alcohol intake, diet, and exercise. PRS categories are shown for descriptive purposes; primary analyses used continuous PRS values.

participants with a diagnosis of SCZ or BD, given that these individuals may exhibit distinct behavioral profiles that could influence the observed associations. Given the heterogeneity of cancer as a diagnostic category, we conducted additional analyses examining seven individual cancer subtypes, i.e. breast, prostate, lung, colorectal, pancreatic, liver, and kidney cancer, selected based on their high incidence or mortality, established associations with modifiable lifestyle factors, and the availability of sufficient incident case numbers in the UK Biobank.

Independent contributions of PRS-SCZ and PRS-BD were formally assessed using likelihood ratio tests comparing the full joint model against models with each PRS dropped in turn. To control for multiple comparisons and reduce the likelihood of false-positive findings, we applied the Benjamini-Hochberg False Discovery Rate (FDR) correction. The resulting FDR-adjusted p-values, referred to throughout as q-values, were considered statistically significant at a threshold of $q < 0.05$. FDR correction was applied separately within each family of analyses. A total of 397 tests were performed across all primary and sensitivity analyses.

All analyses were performed using R programming language [62].

RESULTS

Study population characteristics

The median follow-up period ranged from 13.5 to 13.6 years (IQR: 12.6–14.2), depending on the specific somatic illness under investigation. During this period, we observed a total of 116,072 incident cases of somatic illnesses. Among the 315,313 participants, 4,816 (1.5%) developed dementia, 7,157 (2.3%) developed asthma, 29,824 (9.5%) developed CVD, 2,049 (0.7%) developed IBD, 6,740 (2.1%) developed CLD, 18,931 (6%) developed T2D, 2,615 (0.8%) developed rheumatoid arthritis, 2,024 (0.6%) developed Parkinson’s disease, and 41,916 (13.3%) developed cancer. The number of participants and incident cases included in each complete-case analytic model (which differ from these full-cohort counts owing to model-specific missing-data and prevalent-case exclusions) are presented in Table S3.

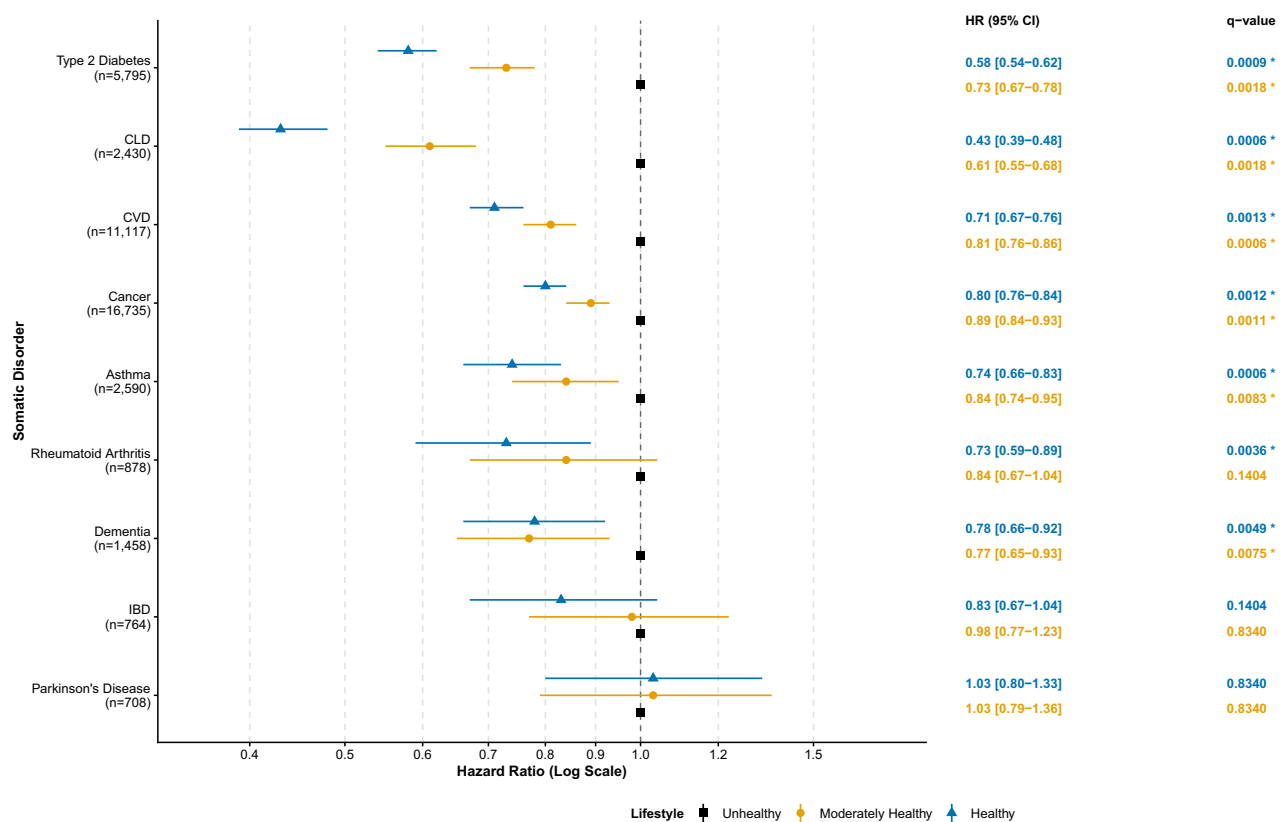


Fig. 1 Associations between Lifestyle Categories and Risk of Somatic Illnesses. Forest plots display hazard ratios and 95% confidence intervals for moderately healthy and healthy lifestyle categories, using the unhealthy category as the reference (HR = 1.0). All models were adjusted for age, sex, education, and employment. Incident cases shown reflect the complete-case analytical sample. q-values shown are FDR-corrected; * $q < 0.05$. IBD, inflammatory bowel disease; CVD, cardiovascular disease; CLD, chronic liver disease.

Baseline demographic and clinical characteristics of the study population ($N = 315,313$) are presented in Table 1, with full characteristics including somatic illness distributions presented in Table S4. The mean age of the total study population was 56.65 ± 8.02 years, and 145,978 (46.3%) of participants were men.

Associations between lifestyle categories and incidence of somatic illnesses

Associations between lifestyle factors and the incidence of somatic illnesses are shown in Fig. 1. HRs, 95% CI, and q-values were calculated for the “Moderately Healthy” and “Healthy” lifestyle categories, using the “Unhealthy” category as the reference (HR = 1). We found significant negative associations between healthy lifestyle and the incidences of several conditions: healthy lifestyle was associated with a significantly lower risk of T2D (HR = 0.58 [0.54 - 0.62], $q = 0.0009$), CVD (HR = 0.71 [0.67 - 0.76], $q = 0.0013$), dementia (HR = 0.78 [0.66 - 0.92], $q = 0.0049$), rheumatoid arthritis (HR = 0.73 [0.59 - 0.89], $q = 0.0036$), asthma (HR = 0.74 [0.66 - 0.83], $q = 0.0006$), CLD (HR = 0.43 [0.39 - 0.48], $q = 0.0006$) and cancer (HR = 0.80 [0.76 - 0.84], $q = 0.0012$) (Table S5).

Associations between individual lifestyle factors and incidence of somatic illnesses

Concerning the associations of individual lifestyle factors with somatic illnesses, we found several significant findings (Table S6). Being a non-smoker and engaging in sufficient regular physical activity was consistently associated with lower risk across multiple conditions. Maintaining a healthy diet was significantly associated with reduced risks for CLD (HR = 0.76 [0.70-0.83], $q = 0.002$), T2D (HR = 0.85 [0.80-0.89], $q = 0.002$), and asthma (HR = 0.86 [0.79-0.93], $q = 0.002$). Although several associations for alcohol consumption reached statistical significance, the hazard ratios

remained close to 1.00, except for CLD, where a significantly reduced risk was observed in individuals with moderate alcohol intake (HR = 0.79 [0.72-0.87], $q = 0.002$).

Associations between genetic risk for SMI and incidence of somatic illnesses

Higher PRS for SCZ was significantly associated with increased risk of asthma (HR = 1.03 [1.00 - 1.06], $q = 0.048$) and dementia (HR = 1.04 [1.01 - 1.08], $q = 0.048$), whereas an inverse association was observed for T2D (HR = 0.95 [0.94 - 0.97], $q = 0.009$) (Fig. 2A).

Higher genetic risk for BD was associated with increased risk of T2D (HR = 1.04 [1.02 - 1.05], $q < 0.001$), with no other significant associations detected across the remaining somatic illnesses (Fig. 2B). Detailed results for the associations between continuous PRS for SCZ and BD and incident somatic illnesses are presented in Table 2.

Likelihood ratio tests confirmed that PRS-SCZ and PRS-BD each contribute independent information to the joint Cox model for T2D ($\chi^2 = 40.30$ and $\chi^2 = 25.28$, respectively, both $q < 0.001$), indicating that the opposing directions of their associations with T2D risk are not driven by shared genetic variance between the two scores. PRS-SCZ also independently contributed to dementia risk ($\chi^2 = 7.03$, $q = 0.048$). Nominal independent contributions of PRS-SCZ to asthma and rheumatoid arthritis ($p = 0.028$ and 0.022 , respectively) did not survive FDR correction. The Pearson correlation between PRS-SCZ and PRS-BD across all participants with both scores ($n = 276,475$) was $r = 0.37$ (95% CI: 0.37–0.38) (Table S7).

Joint effects and interaction models between lifestyle factors and genetic risk for SCZ and BD

Table S8 presents the additive interaction effects of PRS for BD and SCZ with lifestyle factors across nine somatic illnesses, measured using the Relative Excess Risk due to Interaction (RERI)

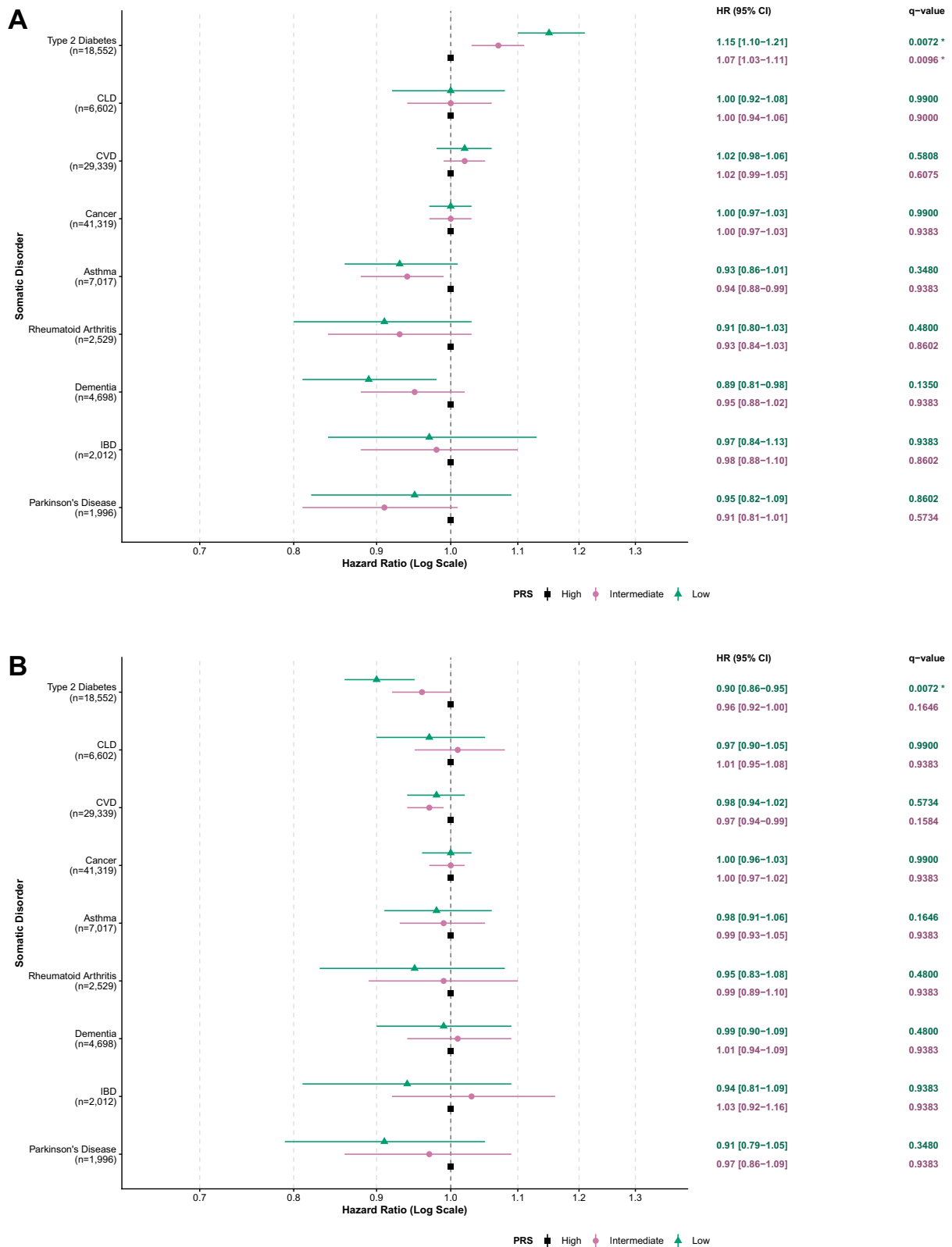


Fig. 2 Hazard Ratios for Associations Between PRS Categories for Schizophrenia. A Bipolar Disorder (B), and Somatic Illnesses. Forest plots display hazard ratios and 95% confidence intervals for combinations of PRS categories (high, intermediate, low) across nine somatic illnesses, with the high PRS category as the reference group (HR = 1.0). PRS categories are shown for visualization purposes only; primary analyses used continuous PRS values, which retain greater statistical power to detect associations. Significant associations reported in the Results reflect continuous PRS analyses. q-values are FDR-corrected; * q < 0.05. All models were adjusted for age, sex, education, employment, and first 10 principal components of ancestry. IBD, inflammatory bowel disease; CVD, cardiovascular disease; CLD, chronic liver disease.

Table 2. Hazard Ratios for the Associations Between PRS for SCZ and BD and Risk of Incident Somatic Illnesses.

Somatic Illness	PRS SCZ			PRS BD		
	HR (95% CI)	p-value	q-value	HR (95% CI)	p-value	q-value
Asthma	1.03 (1.00-1.06)	0.0080	0.0480	1.01 (0.98-1.03)	0.5640	0.7290
Parkinson's	1.02 (0.97-1.07)	0.5250	0.7290	1.03 (0.98-1.07)	0.2270	0.5100
Dementia	1.04 (1.01-1.08)	0.0150	0.0480	1.01 (0.98-1.04)	0.6160	0.7290
CVD	0.99 (0.98-1.00)	0.2070	0.5100	1.01 (1.00-1.02)	0.3040	0.5100
Type 2 Diabetes	0.95 (0.94-0.97)	0.0010	0.0090	1.04 (1.02-1.05)	0.0010	0.0090
Rheumatoid Arthritis	1.05 (1.01-1.10)	0.0230	0.1008	1.00 (0.96-1.04)	0.8120	0.8600
CLD	1.00 (0.97-1.02)	0.6480	0.8640	1.01 (0.98-1.03)	0.6280	0.7290
IBD	1.01 (0.96-1.06)	0.5660	0.7290	1.04 (1.00-1.09)	0.0700	0.2100
Cancer	1.00 (0.98-1.01)	0.3840	0.6910	1.00 (0.99-1.01)	0.5660	0.7290

PRS polygenic risk score, CVD cardiovascular disease, CLD chronic liver disease, IBD inflammatory bowel disease, SCZ schizophrenia, BD bipolar disorder.

Hazard ratios reflect associations per unit increase in continuous PRS. All models were adjusted for age, sex, education, employment, and the first 10 principal components of ancestry. Bold values indicate $q < 0.05$ after Benjamini-Hochberg FDR correction.

and Attributable Proportion (AP). No significant additive interaction was observed after correction for multiple testing.

Figure 3a presents the multiplicative interaction effects of genetic risk for SCZ and lifestyle on the incidence of somatic illnesses. Compared to the high PRS $\times$ unhealthy lifestyle reference group, individuals with low PRS and a healthy lifestyle showed significantly lower risks of CLD (HR = 0.44 [0.35–0.55], $q = 0.003$), T2D (HR = 0.64 [0.55–0.75], $q = 0.003$), CVD (HR = 0.71 [0.62–0.80], $q = 0.002$), and dementia (HR = 0.57 [0.41–0.80], $q = 0.004$).

Figure 3b presents the joint effects of genetic risk for BD and lifestyle. Compared to the high PRS $\times$ unhealthy lifestyle reference group, significant multiplicative interactions were observed for asthma (HR = 0.70, [0.54–0.90], $q = 0.015$), CLD (HR = 0.40, [0.32–0.51], $q = 0.001$), T2D (HR = 0.56, [0.47–0.66], $q = 0.002$), cancer (HR = 0.82, [0.74–0.91], $q = 0.001$), CVD (HR = 0.68, [0.60–0.77], $q = 0.002$), and rheumatoid arthritis (HR = 0.53, [0.36–0.79], $q = 0.006$) for the low PRS $\times$ healthy lifestyle group. Full results of the multiplicative interaction analyses are provided in Table S9 and Table S10.

Results from sensitivity analyses

We conducted several sensitivity analyses to corroborate the robustness of our findings. The results of the sensitivity analysis with the imputed lifestyle dataset confirmed the significant associations found in the unimputed dataset, while also identifying additional significant associations (Figure S2). The additional analysis using a continuous total lifestyle score confirmed the overall protective association of a healthier lifestyle with reduced incidence of somatic illnesses. A dose-response relationship was observed, with progressively lower hazard ratios as the health score increased, particularly for asthma, CVD, T2D, rheumatoid arthritis, CLD, and cancer (Table S11). Sensitivity analysis using a reclassified employment variable distinguishing retired from unemployed individuals yielded lifestyle associations largely consistent with the primary analysis, with all effect directions replicated and hazard ratios differing by no more than 0.05. The associations between PRS-BD and T2D and the inverse association between PRS-SCZ and T2D were replicated. However, the associations between PRS-SCZ and asthma and dementia did not reach statistical significance after FDR correction in this sensitivity analysis (Table S12). Sensitivity analysis excluding participants with a diagnosis of SCZ or BD yielded virtually identical lifestyle associations and fully replicated the PRS-BD and PRS-SCZ associations with T2D. Consistent with the employment reclassification sensitivity analysis, the associations between PRS-SCZ and asthma and dementia did not reach statistical significance after FDR correction (Table S13). Additional analyses

examining seven individual cancer subtypes confirmed the protective association of a healthy lifestyle with reduced risks of the majority of cancer subtypes examined, with the exception of prostate cancer, where a modest increased risk was observed. PRS for BD and SCZ were not significantly associated with risk of any individual cancer subtype after FDR correction (Table S14).

DISCUSSION

To our knowledge, this is the first study to examine both the independent and joint associations of genetic liabilities for SCZ and BD and lifestyle behaviors with the incidence of multiple somatic illnesses. We show that a healthier lifestyle and lower genetic risk for SMI are associated with reduced risks of several somatic illnesses. An inverse association was observed between SCZ genetic risk and T2D, whereby individuals at lower genetic risk for SCZ showed a higher incidence of T2D. Joint analyses further revealed that individuals with both a healthy lifestyle and low genetic risk had the lowest risks of developing somatic illnesses, though no significant additive interaction was observed.

The protective role of a healthy lifestyle in somatic health has been widely recognized [63–67]. In our study those adhering to healthier lifestyle consistently showed lower incidences of T2D, CVD, CLD, asthma, dementia, cancer, and rheumatoid arthritis. These associations, although modest in size, align with an extensive body of research emphasizing the impact of modifiable lifestyle behaviors – i.e. diet, physical activity, smoking, and alcohol use – on a wide range of health outcomes [36, 64, 68, 69]. Here, we used a composite lifestyle score to capture the cumulative impact of health-related behaviors. While individual lifestyle behaviors have been thoroughly studied, their aggregated effect may offer a more effective and accurate prediction of disease risk [29, 69, 70]. This was supported by our results, which showed a clear dose-response pattern; higher lifestyle scores were associated with progressively lower hazard ratios. Rather than acting in isolation, unhealthy lifestyle behaviors may amplify one another through overlapping inflammatory and metabolic pathways. Biological mechanisms underlying these associations are increasingly understood to involve chronic low-grade inflammation [36], mediated by microbiome dysregulation, oxidative stress, epigenetic alterations, and metabolic disruption [35]. Subtype-specific sensitivity analyses further supported these findings, with the protective association of healthy lifestyle consistent across the majority of individual cancer subtypes. A notable exception was prostate cancer, where a modest increased risk was observed, likely reflecting detection bias from higher rates of prostate-specific antigen screening in healthier men [71].

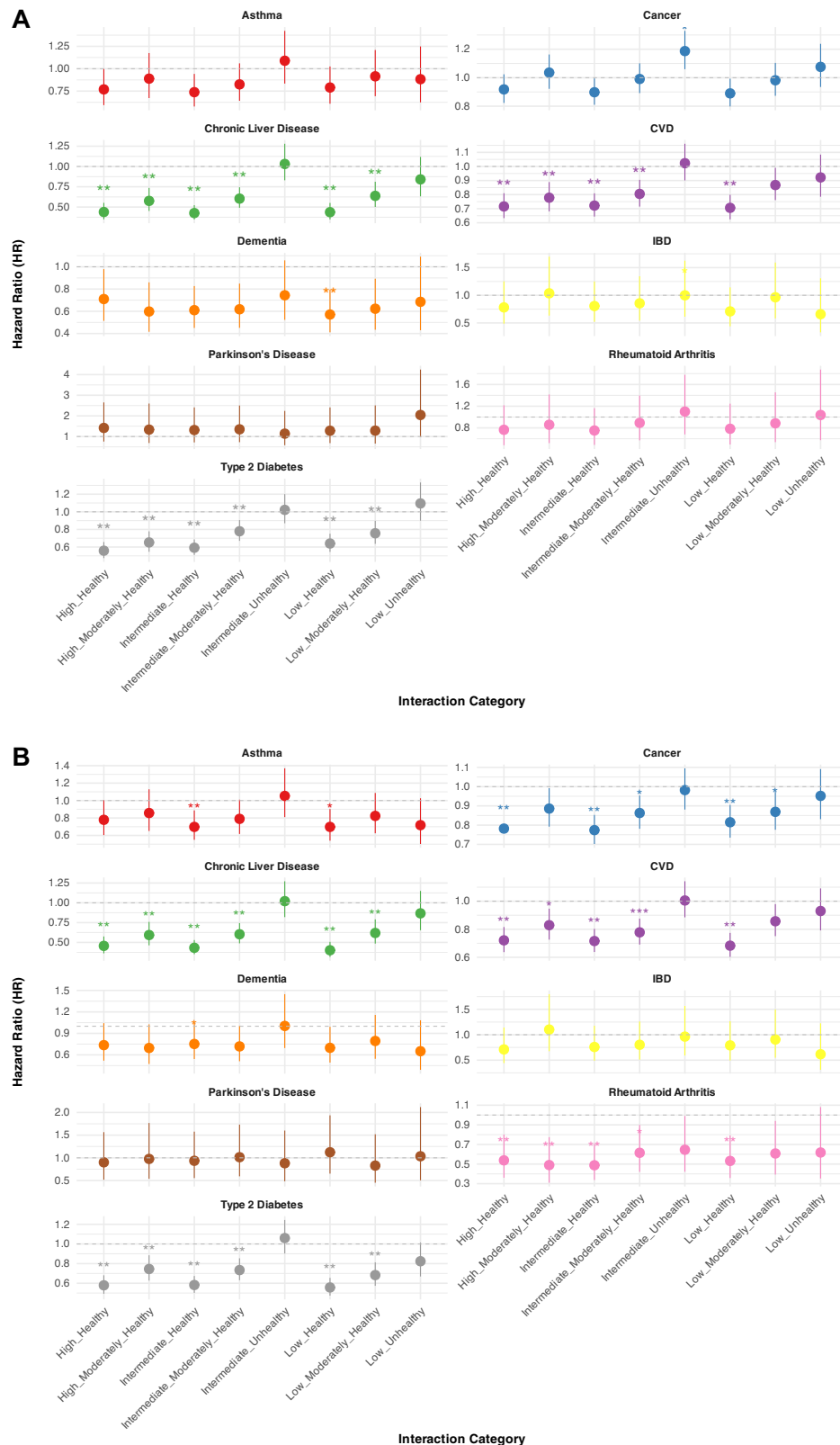


Fig. 3 Joint Associations of PRS and Lifestyle Categories with Somatic Illness Risk. Hazard ratios and 95% confidence intervals are shown for combined PRS $\times$ lifestyle groups relative to the high PRS $\times$ unhealthy lifestyle reference group (HR = 1.0). All models were adjusted for age, sex, education, and employment, and the first 10 principal components of ancestry. Exact q-values for all interaction terms are presented in Table S9 and Table S10. Results are shown separately for PRS-SCZ (**A**) and PRS-BD (**B**). IBD, inflammatory bowel disease; CVD, cardiovascular disease; CLD, chronic liver disease.

Our genetic analyses provide novel insights into the associations between genetic liability for SMI and somatic health. The association between PRS-SCZ and dementia aligns with previous studies [72–75], suggesting a shared genetic basis involving neurodegeneration and accelerated aging, with additional risk attributable to metabolic burden resulting from poor lifestyle and antipsychotic-induced dysregulation [76]. The association between PRS-SCZ and asthma also supports prior research reporting increased risk of autoimmune and inflammatory conditions among individuals with SCZ [77–79]. However, both associations were borderline significant in the primary analysis and did not consistently replicate across sensitivity analyses, suggesting sensitivity to model specification and warranting cautious interpretation. The inverse association between PRS-SCZ and incident T2D is in contrast with some of the previous epidemiological [80] and genetic [51, 81] evidence. Overall, previous literature on the relationship between SCZ and T2D is inconsistent, with several studies aligning with our results [82–88]. Most importantly, two Mendelian randomization studies found evidence of a weak negative genetic correlation and no evidence of a causal relationship between the two conditions in diverse populations [84, 87]. Another UK Biobank study found a significant negative association between PRS-SCZ and T2D, although the findings are based on a partially overlapping sample [85]. Furthermore, Cai et al. [88], employed a series of genomic analysis approaches to explore the genetic association between SCZ and T2D and found a significant negative genetic correlation between T2D and SCZ in a European population. This body of evidence suggests that the relationship between T2D and SCZ may be driven by opposing genetic mechanisms, such as SCZ-associated alleles that correlate with lower BMI, a major genetic risk factor for T2D [89], or by differences in how common versus rare variants contribute to shared genetic architecture [83, 84]. In support of this, likelihood ratio tests confirmed that PRS-SCZ and PRS-BD each contributed independently to T2D risk (both $q < 0.001$), indicating that these opposing associations reflect distinct genetic signals rather than artefacts of score construction. Conversely, the observed positive association between genetic liability for BD and T2D in this study is mostly consistent with prior epidemiological findings [90, 91]. This comorbidity may be explained by several interconnected mechanisms, including chronic low-grade inflammation [92], HPA axis dysregulation, mitochondrial dysfunction, increased insulin resistance [93], oxidative stress, and adverse metabolic effects of psychotropic medications [94–96].

Our multiplicative interaction analyses identified significant interaction terms for the majority of outcomes for both PRS-SCZ and PRS-BD. However, no significant additive interaction was observed after FDR correction across any outcome. This distinction is noteworthy, as multiplicative interactions can arise from the mathematical properties of the scale rather than reflecting a true biological synergy, whereas additive interaction is generally considered the more relevant scale for public health inference [97]. These findings suggest that lifestyle-based prevention strategies are broadly beneficial regardless of genetic risk level, rather than being specifically more effective in individuals at high genetic risk for SMI. Furthermore, the hazard ratios across PRS levels within the same lifestyle category were relatively consistent for the majority of outcomes, suggesting that lifestyle was the primary driver of the observed risk reductions, with genetic risk level contributing relatively little further distinction within lifestyle categories. Although we cannot directly infer effects of lifestyle modifications from a single baseline assessment, these findings highlight the potential of population-wide lifestyle-based prevention for reducing somatic illness risk.

This work has several strengths. It constitutes a comprehensive assessment of the independent and joint effects of polygenic risk for SMI and modifiable lifestyle behaviors, using data from a large, well-characterized cohort with deep phenotyping and rich data on

both genetic and behavioral risk profiles. In addition, stratified analyses and multiple sensitivity checks enhance the robustness and reliability of our findings. Nonetheless, several limitations must be acknowledged. First, the study sample was restricted to individuals of White British ancestry from the UKB, imposing uncertainty on the generalizability of the results to ethnically and geographically different populations. Second, lifestyle factors were based on self-reported data and only assessed at baseline, which may introduce recall bias and fail to capture behavioral changes over time. Furthermore, lifestyle scores exhibited 59% missingness; however, the consistency between our complete-case and multiply imputed results across all outcomes provides direct evidence that this did not materially bias our findings, supporting the robustness of the observed associations regardless of analytical approach. Third, although we adjusted for key socio-demographic variables, residual confounding cannot be entirely ruled out. Follow-up work may include other potentially modifiable factors, such as sleep, body mass index (BMI), social and psychological well-being, to improve predictive accuracy and public health relevance. Finally, a key limitation inherent in most PRS-informed analyses, is the modest variance explained in SCZ and BD liability. To enhance predictive accuracy and better capture the polygenic and pleiotropic nature of mental and somatic comorbidities, future studies could adopt multi-PRS approaches [98, 99].

In conclusion, the present study highlights the role of modifiable lifestyle behaviors and the genomic architecture of complex psychiatric phenotypes in determining susceptibility to somatic illness. These findings underscore the importance of investigating lifestyle-based prevention strategies as broadly applicable approaches to reducing somatic illness burden in those at genetic risk for SMI.

DATA AVAILABILITY

Data utilised in this study are available from the UK Biobank by submitting a data request proposal (<https://www.ukbiobank.ac.uk>).

CODE AVAILABILITY

Codes are available from the corresponding author upon request.

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AUTHOR CONTRIBUTIONS

UI, JL, and MM conceived and designed the study. UI performed the data preparation, data analysis, and interpretation, and drafted the manuscript. BL and NDB contributed to parts of the analysis code. SG, NDB, BR, and DL provided critical revisions of the manuscript. JL and MM supervised the study. All authors reviewed and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The North West Multi-centre Research Ethics Committee provided ethical approval for the UK Biobank project (REC reference: 11/NW/03820). All participants provided written informed consent before recruitment. The present analyses were conducted

using the UK Biobank resource under application number 54176. The study complied with the Declaration of Helsinki.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41398-026-04332-8>.

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