

# Investigating the Demographic, Psychosocial, and Biological Factors Predictive of Long-Term Benzodiazepine Prescription in a UK Biobank Primary Care Cohort: A Machine Learning Approach.

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## Abstract

**Background:** Prevalence of long-term benzodiazepine use is concerning with approximately 300,000 individuals utilising them for over a year in England alone. Adverse implications of prolonged administration are often overlooked by GPs, who prioritise perceived therapeutic efficacy at the detriment of patient well-being. Developing an algorithm identifying at-risk individuals will circumvent unnecessary, prolonged benzodiazepine prescription.

**Methods:** UK Biobank participants with GP prescription data ( $n = 221,999$ ) were used to identify factors of long-term BZD prescription. Cases were matched 1:3 to controls by age and sex. LASSO, elastic net, random forest, and XGBoost were used for prediction stratified by sex and subsequently anxiety status. Important features were selected based on stability scores (regression models) and permutation importance (ensemble methods). Logistic regressions were then performed on salient features to derive odds ratios. Predictive performance of biomarkers were assessed with similar methods.

**Results:** All models showed moderate predictive performance (accuracy = 0.68-0.76, AUC = 0.69-0.73). Anxiety-related variables substantially improved model performance, whilst anxiety and health-related features were consistently selected as important predictors across sexes. Socioeconomic factors were also key predictors for females. Models illustrated limited sensitivity to biomarkers, displaying similar AUCs (0.69-0.72), while biomarker-only models had poor performance (AUC = 0.53-0.56).

**Conclusion:** Models developed accurately classified individuals at risk of prolonged BZD prescription, although biomarkers provided limited discrimination. Integrating such algorithms into primary care systems could help clinicians identify at-risk patients and reduce preventable harms associated with prolonged BZD prescription.

**Keywords:** benzodiazepines, elastic net, LASSO, long-term prescription, machine learning, prediction, random forest, XGBoost.

# 1 Introduction

Benzodiazepines (BZDs) remain one of the most widely prescribed drugs since their inception in the 1950s and the fourth most frequently dispensed pharmacotherapy in the UK, with 1.4 million BZD prescriptions administered in 2017-2018 in England [1]. BZDs are characterised by their ability to potentiate inhibitory neurotransmission via binding gamma-aminobutyric acid type A receptors ( $\text{GABA}_{\text{A}}\text{R}$ 's) throughout the central nervous system, resulting in a diverse range of therapeutic effects. The anxiolytic, hypnotic, and sedative properties of BZDs denote their extensive prescription in primary care – predominantly administered for treatment of anxiety, sleep, and chronic pain disorders [2].

Despite widespread BZD prescription, their use is associated with a range of well documented adverse effects that often pertain to long-term use [3]. Consequently, NICE (National Institute for Health and Care Excellence) guidelines recommend BZD intervention solely for short-term relief (2-4 weeks) [4]. Long-term recipients are not only susceptible to developing psycho-physical BZD dependency and tolerance, but also cognitive impairment, dementia, withdrawal, and tendency for drug misuse [5-8]. Concerningly, Kroll et al. (2016) reveals that individuals prescribed BZDs in primary care settings often possess characteristics predisposing them to these harsh side effects [9]. Nonetheless, BZDs are still liberally prescribed long-term, with 44% prescriptions in 2017 given beyond the recommended 4 weeks [10] and 35% of recipients in England using them for >1 year [11].

Factors associated with BZD use are well documented in literature, with discrepancies in prescription patterns between age groups, sex, and socioeconomic strata all prevalent. Females are almost twice as likely to be prescribed BZDs [12], with male clinicians preferentially administering BZDs to women at higher doses [13]. Soyombo et al. (2020) also found deprivation to be associated with higher rates of BZD prescription in the UK [14]. Long-term repeat BZD use occurs disproportionately among individuals with physical and/or psychiatric comorbidities, low income, receiving social benefits, a history of opioid or BZD use, and notably in elderly individuals [15-17].

Machine learning (ML) leverages large ascale data and statistical algorithms to generate predictive models, which are capable of capturing complex non-linear relationships and dealing with extensive feature sets [18]. For instance, random forest (RF) and support-vector machine approaches were utilised to predict advent and quantity of BZD prescription in individuals with high discrimination [19]. Similarly, ML algorithms have been successfully deployed to classify individuals at risk of sustained prescription drug use, as in the case of postoperative opioid administration [20, 21].

Kinney et al. (2023) emphasises the need of a predictive algorithm tailored toward identifying individuals susceptible to long-term BZD use. Whilst research has elucidated the risk factors of BZD use from an epidemiological perspective, and separately utilised ML to predict drug prescription, duration, and quantity, a methodology has not been developed to classify individuals likely to receive long-term BZD prescription. Additionally, susceptibility to BZD use is yet to be explored via a biomarker-based standpoint.

This study therefore aims to develop an ML classification algorithm for accurate prediction of prolonged BZD use in a primary care UK Biobank population, utilising prescription frequency as a proxy for long-term prescription. Specifically, we aim to harness the joint power of demographic, environmental, and behavioural factors to predict sustained BZD use. We also aim to develop a classification model comprising a panel of biomarkers, which may shed light on underlying biomechanisms and implicated biological factors. Given BZDs are most often prescribed for anxiety treatment [22], we also endeavour to assess if stratifying individuals based on medical history of anxiety alters overall predictive accuracy.

Amid prevailing reluctance surrounding BZD prescribing within the GP community [23], identification of individuals at risk of long-term BZD use will further enhance clinical decision

making. In high-risk individuals alternative therapeutic approaches may be explored, or if BZD prescription is unavoidable, enhanced patient surveillance and check-up can be enacted. Not only would this improve clinician confidence in prescribing, but also patient safety, by mitigating inappropriate prescription to those most vulnerable to prolonged BZD use and harmful side effects.

## 2 Methods

### 2.1 Data Source

Data was sourced from the UK Biobank - a prospective cohort study with deep genetic and phenotypic data collected on 502,211 individuals from across the United Kingdom between 2006 and 2010 [24], aged between 40 and 69 at recruitment. Biobank data was combined with general practitioner (GP) prescription records. These records contain detailed information on all NHS prescriptions issued by GPs and affiliated non-medical prescribers and dispensed in the community across the UK. Each record includes the number of items prescribed, total cost, and quantity, identified by British National Formulary (BNF) codes [25].

### 2.2 Inclusion and Exclusion Criteria

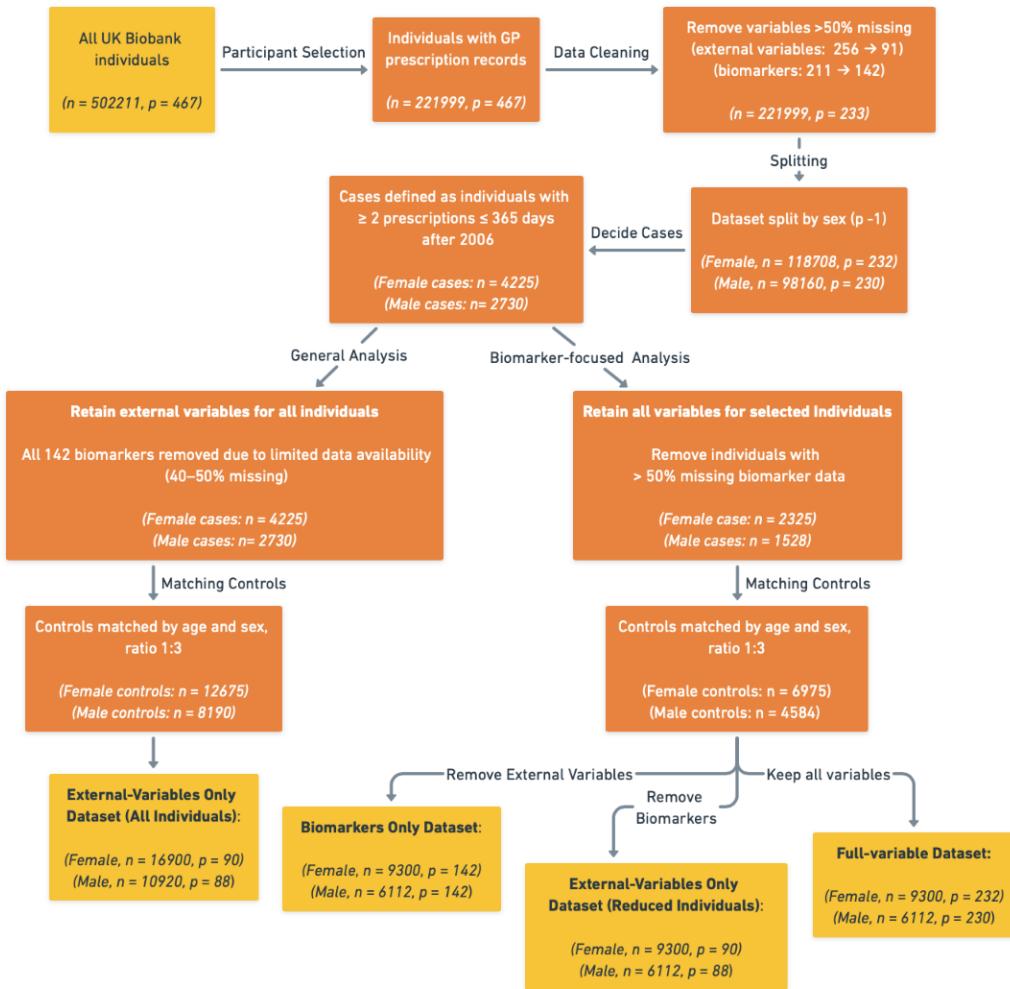
This nested case-control study excluded prevalent cases alongside individuals who had long-term benzodiazepine prescriptions prior to 2006, when UK Biobank data collection began. This ensured that all measured exposures temporally preceded the outcome, minimising the risk of reverse causality. Individuals who had no history of GP prescription were also excluded as they may not use health services frequently and may systematically differ in behaviours and exposures. Participation in the UK Biobank and existence of linked GP prescription data were required for inclusion, amounting to 221,999 participants. We selected 467 variables for analysis based on their potential relevance to prescription behaviour. After removing variables with a missing rate greater than 50%, 233 variables remained, including demographics, lifestyle, mental health, clinical factors, environmental exposures, and biomarkers. Only baseline measurements were retained to ensure no duplicate measurements for a given individual.

### 2.3 Dataset Construction and Data Preparation

To explore gender-specific patterns, we stratified data by sex. Two additional sex-specific variables ('menopause' and 'contraceptive pill') were included in the female dataset. We defined cases as individuals who had received two or more BZD prescriptions within 365 days, while controls were those who did not meet this criterion. Based on this definition, a total of 6,955 individuals were identified as cases, including 4,225 females and 2,730 males. The remaining 215,044 individuals constituted the control pool. For general analysis, biomarkers were removed due to lack of biomarker data for more than 45% of individuals. Controls were matched to cases in a 1:3 ratio by age and sex. The final datasets for the general analysis included 16,900 females and 10,920 males.

We evaluated the predictive power of anxiety related variables by comparing the performance of the models with and without these predictors. We further conducted an additional analysis stratified by anxiety status within the study population. Anxious individuals were defined as participants who reported visiting a general practitioner (GP) and/or a psychiatrist for nerves, anxiety, tension, or depression. This subgroup comprised 7,836 anxious females and 9,064 non-anxious females, as well as 3,441 anxious males and 7,479 non-anxious males.

To investigate possible biological predictors, we conducted an analysis focusing on biomarkers. Individuals with a biomarker missing rate greater than 50% were excluded. The number of cases were reduced to 2,325 females and 1,528 males, with the final sample including 9,300 females and 6,112 males. These individuals were used to construct three models based on



**Fig. 1** Flowchart: Overview of data preprocessing and analysis pipeline (n = number of individuals; p = number of variables)

different variable sets: (i) biomarkers only, (ii) non-biomarker variables, and (iii) all variables combined. This design enabled a direct comparison of the predictive power of biomarkers.

During data preprocessing, select categorical variables were recoded and factor levels merged, aiding model interperetability and generalisability. The various datasets were randomly split into training (80%) and test (20%) sets. Missing values were imputed separately within each set. Before imputation participant identifiers (eid) and sex were removed from the dataset. The MissForest algorithm was utilised for imputation of the training data, from which MissForest was trained and subsequently used to impute missing values in the test set. This procedure ensured that the training and test datasets remained independent during preprocessing, preventing data leakage. For LASSO and elastic net models, continuous variables were standardised and categorical variables were transformed using one-hot encoding.

## 2.4 Modelling Approaches

Descriptive analyses summarised characteristics of the study population and statistical tests were applied to compare differences between groups. All variables were stratified by case-control status and sex. For continuous variables, Wilcoxon rank-sum tests were used; for

categorical variables, chi-squared tests were applied. A p-value < 0.05 was considered statistically significant. Number and type of BZD prescription can be found in supplementary table S.2.

For predictive modeling of long-term BZD prescription, we constructed four supervised ML models: LASSO regression, elastic net (ElNet) regression, random forest, and XGBoost. All models were trained and evaluated by gender subset to capture possible gender-specific patterns. The LASSO hyperparameter  $\lambda$  that controls regularisation strength was tuned via 10-fold cross-validation. To evaluate the stability of the selected predictors, we conducted stability selection and then used the stably selected variables in the logistic regression model to obtain odds ratios.

Given LASSO may miss essential predictors when variables are highly correlated, elastic net regression was used, addressing this limitation. This method combines L1 and L2 regularisation terms and applies to dealing with multicollinearity among variables. The mixed parameter  $\alpha$  is tuned by optimisation over the interval [0,1] and selected through 10-fold cross-validation, aiming to maximize the AUC (area under curve), alike tuning of the regularisation parameter  $\lambda$ . After the models are fitted, stability selection [26] is carried out on variables with non-zero coefficients.

Two ensemble methods explored possible non-linear relationships and investigated feature selection using permutation importance. Random forest hyperparameters (*see supplementary materials S.4*) were optimised through a cross-validation algorithm minimising the out-of-bag error, enabling selection of informative variables. Finally, we constructed the XGBoost model, which is based on gradient boosting - a method that utilises residual errors to fit subsequent models. During training, predefined parameters were set (*see supplementary material S.4*). These parameters were tuned by 10-fold cross validation to maximise the AUC. The model was trained using the binary logistic objective function, and predictions on the test set were thresholded at 0.5 to classify outcomes. Biomarker analyses were only evaluated with LASSO and random forest approaches.

Model evaluation was based on the area under the curve (AUC) as the main indicator to measure the overall predictive ability of the model. All statistical analyses and ML models were implemented using R version 4.4.1 and Python version 3.11.4 .

## 3 Results

### 3.1 Population Characteristics

There were 4,225 female and 2,730 male cases, with an additional 12,675 female and 8,190 male controls, matched randomly by age and sex (*see Table 1*). The cohort had a median age of 58 years old (IQR = 50-63) for females and 59 years old (IQR = 51-64) for males, and comprised predominantly white individuals. In comparison to the control groups, cases had significantly higher levels of unemployment, lower home ownership rates, poorer general health, and more frequent reports of anxiety, tension, and irritability.

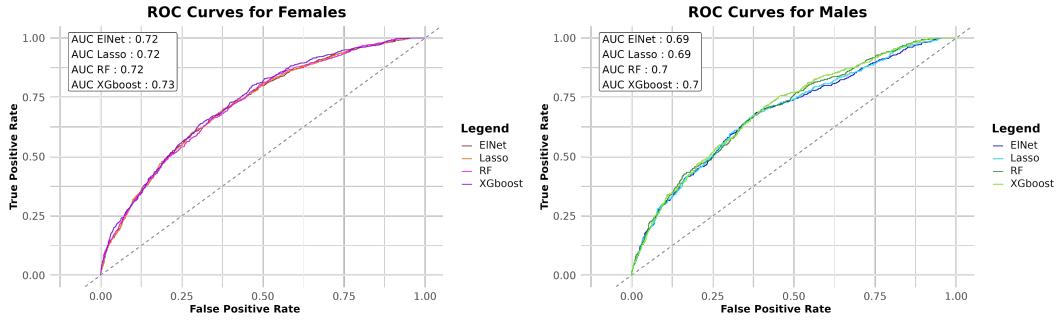
Analysis of BZD prescriptions revealed substantial differences between cases and controls. Over 90% of both female and male controls have never been prescribed BZDs, while over 65% of cases in each group had three or more prescriptions (*see Supplementary material S.2*). Among the 16 identified types of BZDs from GP prescription data, diazepam, temazepam, clonazepam and lorazepam were the four most commonly prescribed medicines, collectively accounting for over 90% of total prescriptions. Diazepam usage was proportionally more common in control groups compared to cases. Male cases had a higher average prescription count per person (9.89) compared to female cases (8.66).

**Table 1** Comparison of baseline characteristics between cases and controls stratified by sex. Median (IQR) for (skewed) continuous variables and N (%) for categorical variables were shown. P-values were derived from Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables. \* denotes p-values < 0.05, \*\* denotes p-value < 0.01, \*\*\* denotes p-value < 0.001.

	Female (n = 16,900)			Male (n = 10,920)		
	Case n = 4,225	Control n = 12,675	p-value	Case n = 2,730	Control n = 8,190	p-value
<b>Sample characteristics</b>						
Demographics						
Age at recruitment	58.0 (50.0–63.0)	58.0 (50.0–63.0)	0.993	59.0 (51.0–64.0)	59.0 (51.0–64.0)	0.974
Ethnicity = White	4,021 (95.6)	12,042 (95.4)	0.613	2,600 (95.8)	7,772 (95.4)	0.411
Owner or rent			***			***
Own	3,544 (88.6)	11,305 (93.7)		2,228 (87.9)	7,238 (93.0)	
Rent	435 (10.9)	668 (0.8)		285 (11.2)	471 (6.1)	
Others	20 (0.5)	96 (0.8)		22 (0.9)	74 (1.0)	
Unemployed	2,218 (53.1)	5,855 (46.6)	***	1,375 (51.0)	3,348 (41.3)	***
External variables						
Home area population density			**			*
Urban	3,613 (86.5)	10,619 (84.6)		2,328 (86.6)	6,822 (84.5)	
Small Town	328 (7.9)	1,080 (8.6)		214 (8.0)	720 (8.9)	
Village	153 (3.7)	558 (4.4)		91 (3.4)	343 (4.2)	
Rural	34 (0.8)	80 (0.6)		19 (0.7)	40 (0.5)	
Hamlet and Isolated Dwelling	50 (1.2)	215 (1.7)		37 (1.4)	153 (1.9)	
Education score	6.8 (1.2–19.3)	7.7 (1.9–19.8)	***	7.6 (1.6–22.1)	8.0 (2.0–20.8)	0.268
Income score	0.12 (0.06–0.33)	0.11 (0.05–0.3)	***	0.11 (0.06–0.28)	0.11 (0.05–0.3)	0.524
Employment score	0.07 (0.05–0.12)	0.08 (0.05–0.13)	***	0.07 (0.05–0.12)	0.08 (0.05–0.14)	***
Crime score	0.01 (-0.50–0.52)	-0.05 (-0.58–0.47)	***	0.03 (-0.50–0.53)	-0.01 (-0.53–0.50)	*
Housing score	18.4 (11.1–27.3)	17.4 (10.2–25.8)	***	18.0 (10.7–26.4)	17.4 (10.1–25.8)	**
IMD score	13.7 (7.6–25.2)	12.6 (7.0–22.2)	***	13.7 (7.4–26.4)	12.7 (7.2–23.1)	***
Living environment score	15.4 (7.4–27.0)	14.37 (7.2–25.8)	*	15.8 (7.8–27.0)	14.1 (7.2–26.1)	**
Mental health variables						
Anxiety / anxious individuals	2,747 (65.7)	5,060 (40.3)	***	1,320 (48.9)	2,114 (26)	***
Health score	-0.05 (-0.6–0.49)	-0.01 (-0.57–0.6)	***	-0.04 (-0.6–0.54)	0.03 (-0.53–0.65)	***
Overall health rating			***			***
Poor	387 (9.2)	459 (3.6)		376 (13.9)	409 (5.0)	
Fair	1,191 (28.4)	2,417 (19.2)		812 (29.2)	1,855 (23.1)	
Good	2,220 (52.9)	7,491 (59.5)		1,257 (46.5)	4,620 (56.7)	
Excellent	396 (9.4)	2,231 (17.7)		259 (9.6)	1,266 (15.5)	
Worrier / anxious feelings = Yes	3,072 (74.7)	7,735 (62.8)	***	1,565 (58.6)	3,697 (46.6)	***
Tense / 'highly strung' = Yes	1,324 (33.0)	2,172 (17.8)	***	688 (26.3)	1,188 (15.0)	***
Irritability = Yes	1,340 (33.3)	3,083 (25.5)	***	1,054 (40.9)	2,333 (30.0)	***

### 3.2 Sex Stratified Analysis

To gain a comprehensive understanding of predictive patterns and variable importance, we evaluated the four different ML models. Across all models and sexes, the performances were comparable (*see figure 2*). Only the random forest model showed substantially higher sensitivity and displayed a superior ability to distinguish true positive cases, alluding to a model with attractive facets for clinical use (*table 2*). However, this could be due to the majority voting threshold used. The models consistently showed slightly higher AUCs for females, (~ 2%) than for males. This difference may be influenced by the larger number of females, which provided more predictive power.



**Fig. 2** ROC curves of elastic net, LASSO, random forest, and XGBoost models predicting prolonged BZD prescription, stratified by sex.

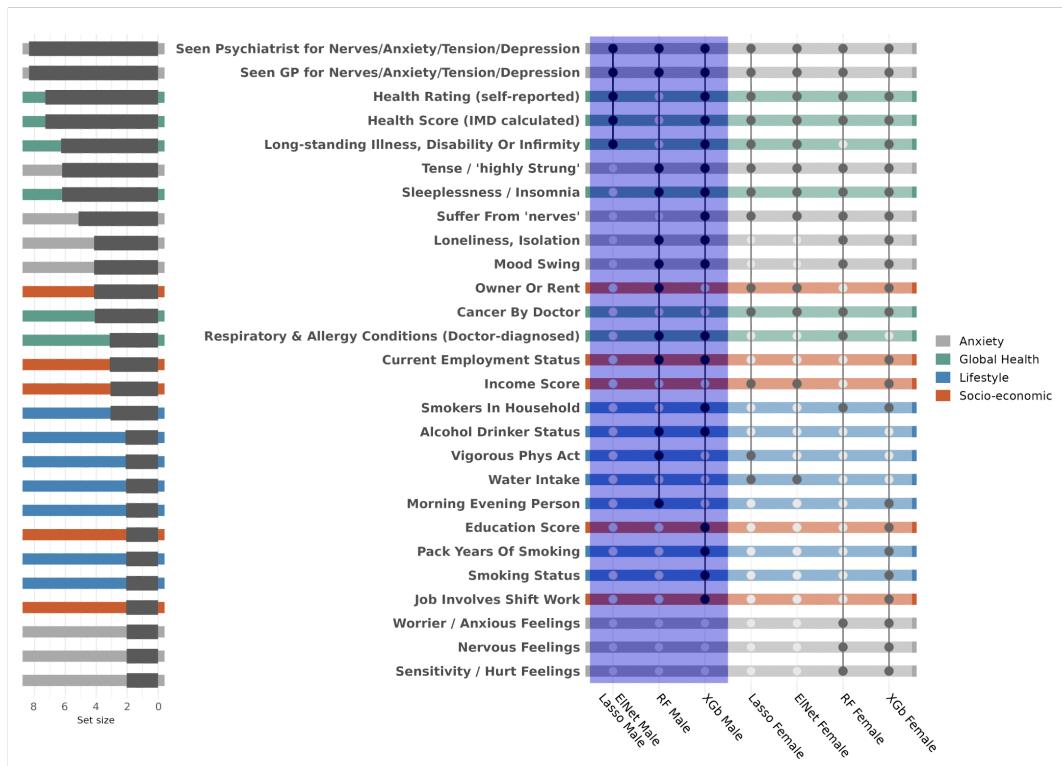
**Table 2** Performance metrics (AUC, Accuracy, Sensitivity, Specificity, F1 Score) by model and gender.

Sex	Model	AUC	Accuracy	Sensitivity	Specificity	F1 Score
Female	Lasso	0.72	0.76	0.10	0.98	0.17
	Elastic Net	0.72	0.76	0.11	0.98	0.19
	Random Forest	0.72	0.68	0.58	0.71	0.61
	XGBoost	0.73	0.76	0.10	0.98	0.17
Male	Lasso	0.69	0.76	0.08	0.98	0.14
	Elastic Net	0.69	0.76	0.10	0.98	0.17
	Random Forest	0.70	0.69	0.49	0.75	0.55
	XGBoost	0.70	0.75	0.11	0.97	0.19

The variable importance for each model and sex subgroup is summarised in the UpSet plot (Figure 3). We applied model-specific criteria to define “predictive” variables: for LASSO and elastic net, we selected variables with high stability scores (achieved by tuning the penalty parameter and selection proportion for multiple resamples); for random forest, we included features with positive permutation importance; and for XGBoost, those with gain values above the third quartile of all gains.

Given that BZDs are commonly prescribed for anxiety-related conditions, we paid particular attention to such variables. Nine anxiety-related variables were selected in at least two models. Notably, two features were selected across all models: ‘seen psychiatrist’ and ‘seen GP for nerves/anxiety/tension/depression’. Other consistently important variables were health-related, including ‘health rating’, ‘health score’, ‘long-standing illness, disability or infirmity’ and ‘sleeplessness/insomnia’. Sex-specific patterns in variable selection were observed. Socioeconomic indicators appeared more predictive among females, with ‘income score’ and housing status (‘own or rent’) each selected three times. In contrast, ‘alcohol drinker status’ was predictive only among males.

Women also had a greater number of anxiety-related predictors, with three additional variables selected in ensemble models, suggesting a stronger role of anxiety in predicting long-term prescriptions in females. Model architecture also influenced variable selection. Ensemble methods tended to prioritise a broader range of anxiety-related features — such as ‘lonelessness/isolation’ and ‘mood swings’ — while regression-based models (LASSO and elastic net) placed greater emphasis on health and socioeconomic factors, selecting fewer anxiety-related variables (two for males and four for females). Notably, XGBoost was the only model that selected individual smoking-related variables in both sexes, specifically ‘pack years of smoking’ and ‘smoking status’.



**Fig. 3** Upset plot for the different models and sex. Set size represents the number of models in which a given variable was selected. Only variables selected by at least 2 models are shown.

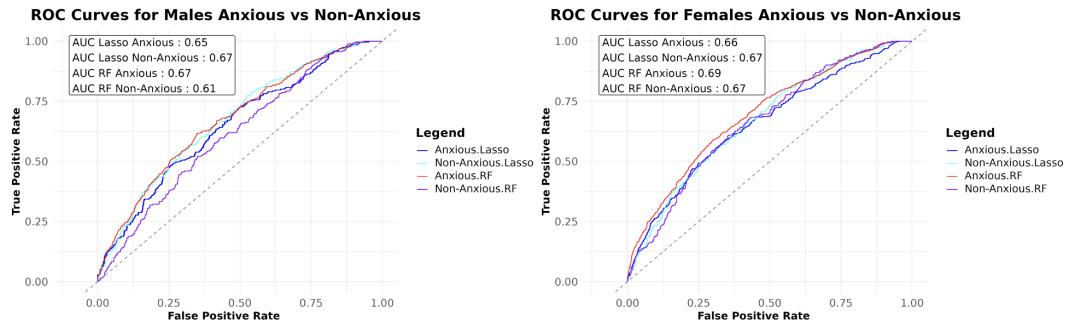
To assess the specific contribution of anxiety related variables (*see supplementary material S.8*), random forest and LASSO models were run excluding these predictors. This exclusion resulted in a decrease in AUC of approximately 4–5% across both models and sexes (AUCs: 0.65 for males and 0.68 for females) (*see supplementary material S.6*). This finding confirms the significant predictive value of anxiety-related variables for long-term BZD prescriptions. However, even in their absence, other factors, particularly health-related variables, still provided a modest level of predictive accuracy. These anxiety-related variables may also exhibit stronger predictive power specifically among individuals with anxiety, suggesting the potential value of stratifying analyses by anxiety status.

### 3.3 Determining Predictive Power in Anxious Individuals

Following an initial comparison in four models, LASSO and random forest were selected for additional analysis, examining their predictive power in the anxious group, stratified by sex.

Among males, LASSO achieved an AUC of 0.65 for anxious individuals and 0.67 for non-anxious individuals (Figure 4). This indicates marginally better predictive performance in the non-anxious group. In contrast, random forest showed stronger performance in the anxious subgroup (AUC = 0.67), compared to non-anxious (AUC = 0.61) (Figure 4). Among females, LASSO resulted in a similar AUC for both anxious (0.66) and non-anxious (0.67) individuals (Figure 4). Random forest showed marginally better performance in the female anxious subgroup (AUC = 0.69) compared to the non-anxious group (AUC = 0.67).

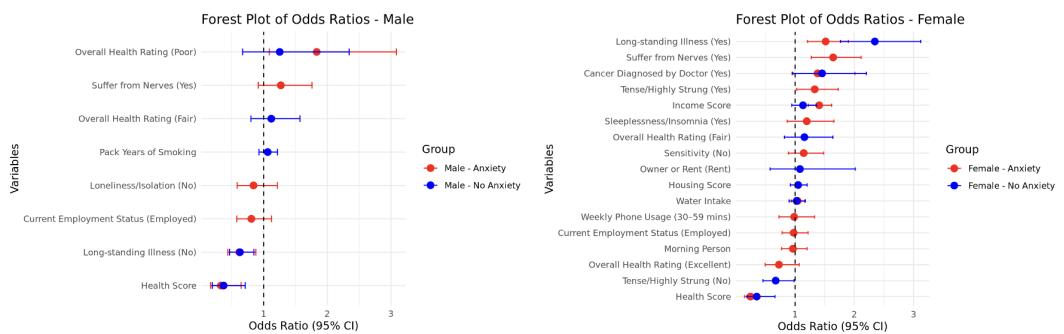
Logistic regression was used to evaluate the strength and direction of associations for variables selected via LASSO stability selection. Forest plots were used to visualise the odds ratios (ORs) and confidence intervals (CIs) for males and females, stratified by anxiety status (Figure 5).



**Fig. 4** ROC curves for LASSO and random forest models predicting long-term BZD prescriptions, stratified by sex and anxiety status.

Two health-related variables, the ‘health rating’ and the ‘health score’ were frequently selected between subgroups. The ‘health rating’ variable is a subjective self-reported measure of general health; while the ‘health score’ is an area-level index that combines measures of mortality, morbidity, disability, and mental health burden.

In anxious males, individuals reporting poor health were 83% more likely to receive long-term BZD prescriptions ( $OR = 1.83$ , 95% CI: 1.09–3.11,  $p = 0.022$ ), while those with a ‘long-standing illness’ were 38% less likely ( $OR = 0.62$ , 95% CI: 0.44–0.88,  $p = 0.007$ ). A higher ‘health score’ was associated with a 67% reduction in the odds of prolonged prescribing ( $OR = 0.33$ , 95% CI: 0.16–0.59,  $p = 0.001$ ). In non-anxious males, long-standing illness and better ‘health scores’ were also associated with lower odds of sustained prescribing ( $OR = 0.63$ , 95% CI: 0.47–0.85,  $p = 0.002$  and  $OR = 0.37$ , 95% CI: 0.18–0.64,  $p = 0.003$  respectively). Other predictors such as ‘smoking history’ and ‘fair health rating’ showed positive trends but were not statistically significant (*see supplementary material S.7*).



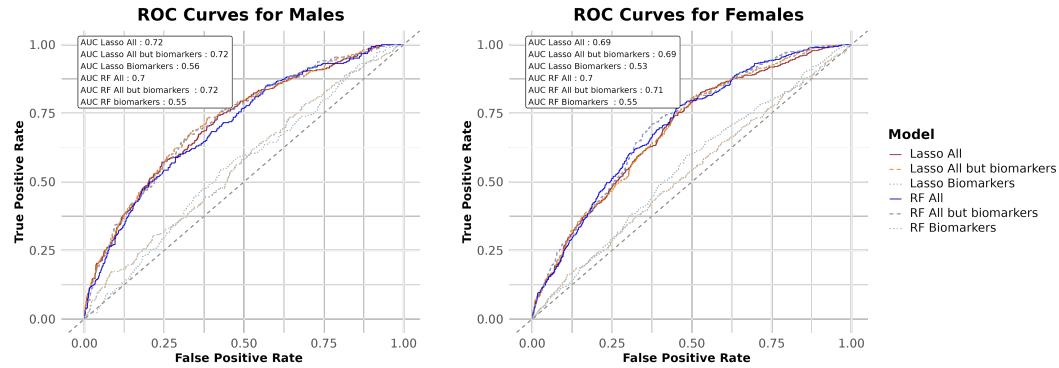
**Fig. 5** Odds ratios from logistic regression on stably selected variables predicting prolonged BZD prescriptions, stratified by sex and anxiety status.

In anxious females, being ‘tense or highly strung’ and ‘suffering from nerves’ were associated with 33% and 64% higher odds of long-term BZD use, respectively ( $OR = 1.33$ , 95% CI: 1.03–1.73,  $p = 0.031$  and  $OR = 1.64$ , 95% CI: 1.28–2.12,  $p < 0.001$ ). ‘Long-standing illness’ increased the odds by 52% ( $OR = 1.52$ , 95% CI: 1.21–1.90,  $p < 0.001$ ), and higher income scores were also positively associated (41% more likely,  $OR = 1.41$ , 95% CI: 1.23–1.62,  $p < 0.001$ ). Behavioural factors like ‘phone usage’ and not ‘being a morning person’ were selected but were not statistically significant. In non-anxious females, long-standing illness more than doubled the odds ( $OR = 2.35$ , 95% CI: 1.76–3.12,  $p < 0.001$ ), while those who were not ‘tense or highly strung’ were 33% less likely to have prolonged prescriptions ( $OR = 0.67$ ,

95% CI: 0.46–0.99,  $p = 0.041$ ). Better ‘health scores’ remained protective, reducing odds by 65% (OR = 0.35, 95% CI: 0.18–0.60,  $p = 0.001$ ). This suggests that individuals living in healthier communities are less likely to receive long-term prescriptions, reflecting differences in overall healthcare need, access, or prescribing behaviors (*see Supplementary material S.7 (Table 5 and 6)*).

### 3.4 Determining Predictive Power of Biomarkers

We further examined the ability of biomarkers in predicting individuals likely to receive long-term BZD prescription across three related datasets.



**Fig. 6** ROC curves of LASSO and random forest models, using datasets that include: all variables, all variables except biomarkers, and only biomarkers. The datasets are stratified by sex.

This analysis revealed that biomarkers alone had limited predictive power in both sexes and across both models, with AUC values around 0.55 (only marginally better than chance). Interestingly, models that excluded biomarkers performed as well as, or slightly better than, those that included them in addition to all other predictors. This suggests that the inclusion of biomarkers may dilute the predictive signal rather than enhance it. Overall, for prediction of long-term prescriptions of BZDs for both gender, biomarkers do not contribute when used in conjunction with other variables for prediction, reflecting the fact that biomarkers likely proxy for underlying information captured by non-biomarker variables.

## 4 Discussion

BZDs remain widely prescribed despite the risks of long-term use, creating significant public health challenges [3]. Many demographic, clinical, and socioeconomic predictors of BZD prescription have been identified previously [12, 14, 16]; however, there is still an unmet need for a predictive algorithm specifically identifying individuals at risk for long-term BZD use. Our study addresses this gap by developing and evaluating multiple ML algorithms (LASSO, elastic net, random forest, XGBoost) to classify individuals who are likely to receive long-term BZD prescriptions, using data from the UK Biobank.

Our results indicate that all ML models achieved moderate to good predictive performance, with AUC values ranging between 0.69 and 0.73. Consistent with existing research [19, 20], ensemble methods showed marginally superior performance in capturing complex and non-linear relationships within the data. This supports their potential use in clinical settings. Excluding anxiety-related variables reduced model performance as expected, highlighting their role in the prediction of prolonged BZD prescriptions.

Anxiety status alone did not appear to significantly alter model performance, suggesting it is not the sole driver of sustained BZD use. Instead, broader clinical and structural factors underlie long-term BZD prescribing. Specifically, both clinical burden and structural

health inequalities, including socioeconomic disadvantage, emerged as key drivers across both sexes, regardless of anxiety history. Among individuals with anxiety, additional layers such as behavioural traits and mental health indicators further shaped prescribing patterns. This highlights the complex nature of BZD prescribing risk and supports the development of more nuanced, multi-dimensional risk models for clinical use.

Biomarkers measured at baseline provided only marginal discrimination of long-term BZD prescribing and did not enhance the performance of models built from demographic, environmental and psychological variables. Biomarker data from the UK Biobank had substantial missingness, limiting the number of biological factors that could be assessed. Among the biomarkers with sufficient completeness, most were general haematology and routine clinical chemistry measures. These biomarkers do not directly reflect GABA<sub>A</sub>R function, neurosteroid tone, or BZD pharmacokinetics, so any association with long-term prescribing is likely indirect, mediated by factors such as age, multimorbidity, or social deprivation. This finding accords with UK and international prescribing guidelines, which prioritise symptom severity and duration, comorbidity, and socioeconomic context before initiating BZDs. Previous studies also indicate that clinical and socioeconomic features dominate predictions of BZD prescribing patterns. The limited incremental predictive value offered by the available biomarkers likely reflects their non-specificity, collinearity with established predictors, and the overriding role of clinical judgement in prescribing decisions. Although our results suggest that widespread biomarker screening is unlikely to be a cost-effective approach to identify individuals at higher risk of prolonged BZD use, future investigations may benefit from exploring targeted biological markers, such as CYP-related phenotypes involved in diazepam metabolism or stress-axis hormones such as cortisol [27, 28].

From a clinical perspective, our findings support the use of predictive models to identify patients at increased risk of long-term BZD use. Such models could facilitate targeted interventions, including alternative therapeutic approaches, enhanced patient monitoring, or educational support to both patients and doctors. Given that inappropriate long-term BZD use can result in significant patient harm [4, 6, 7], predictive models integrated into GP workflows could significantly improve prescribing practices and patient safety.

Nevertheless, our study is subject to several limitations. Firstly, our case definition of repeated BZD prescriptions could be considered ambiguous. Individuals receiving a single repeat prescription within a year and individuals receiving two separate prescriptions for unrelated incidents would both be classified as cases under our definition. Secondly, our models were validated internally, which typically overestimates prediction accuracy. External validation in independent populations is therefore important to confirm model generalisability. Furthermore, the predominantly white and older UK Biobank participants may further limit the generalisability of our findings to more diverse populations.

Therefore further research should prioritise validating these predictive algorithms externally using data from diverse populations. This could help uncover differences in BZD prescribing patterns across age groups and countries. Additionally, the ambiguity of case definition could be addressed by ascertaining additional data containing detailed prescription metrics, such as dosage and cause of prescriptions, which could help the identification of true cases of long-term BZD use.

Enhanced predictive models could substantially improve clinical decision-making, increasing clinician confidence and patient safety by identifying high-risk individuals and facilitating targeted interventions or alternative therapies. Specifically tailoring models to detect those at increased risk of drug misuse or addiction would be a huge step forward to achieve personalised medicine practices within GP settings. However, rigorous testing is needed, including thorough impact analyses, to ensure these algorithms effectively change clinical outcomes and meaningfully reduce unnecessary BZD use.

## **Author Contributions**

### **To the Overall Study**

Conceptualisation: D.R., B.P. Study Design: D.R., B.P, T.G, W.F, Y.C. Data Preprocessing: D.R., T.G, W.F. Descriptive analysis: Y.C. LASSO : D.R. Elastic net analysis: B.P. Stability selection: D.R., B.P. Random forest and XGBoost: T.G. Logistic Regression: B.P.

### **To the Write-Up**

Abstract: D.R., Y.C. Introduction: D.R.. Methods: W.F. Results: B.P, T.G, Y.C. Discussion: B.P., Y.C.

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## **Appendices**

Supplementary materials can be found at the end of the report.

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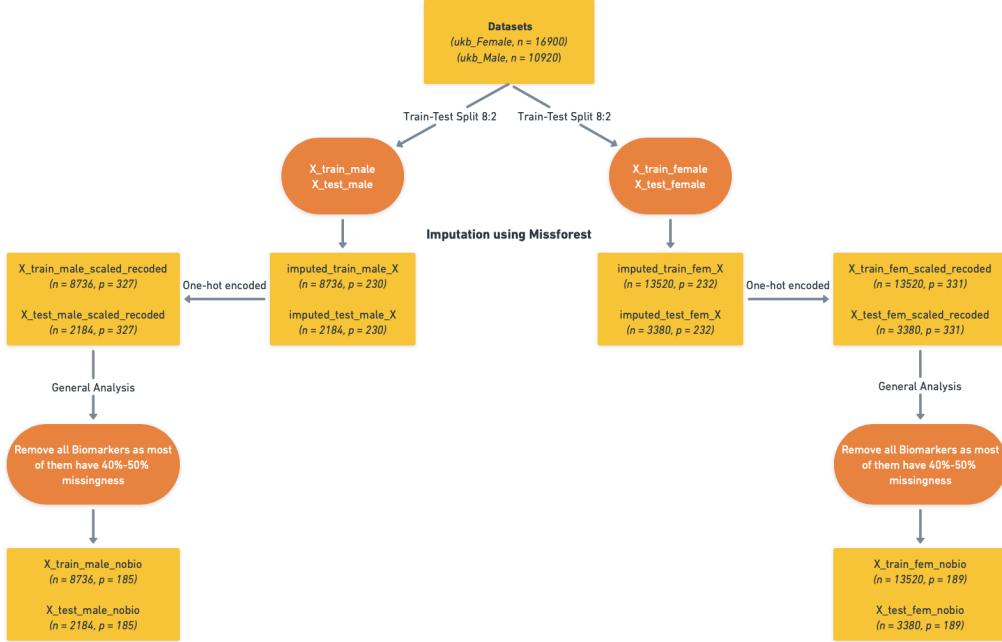
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## Supplementary Materials

### S.1 Dataset Preparation for Machine Learning



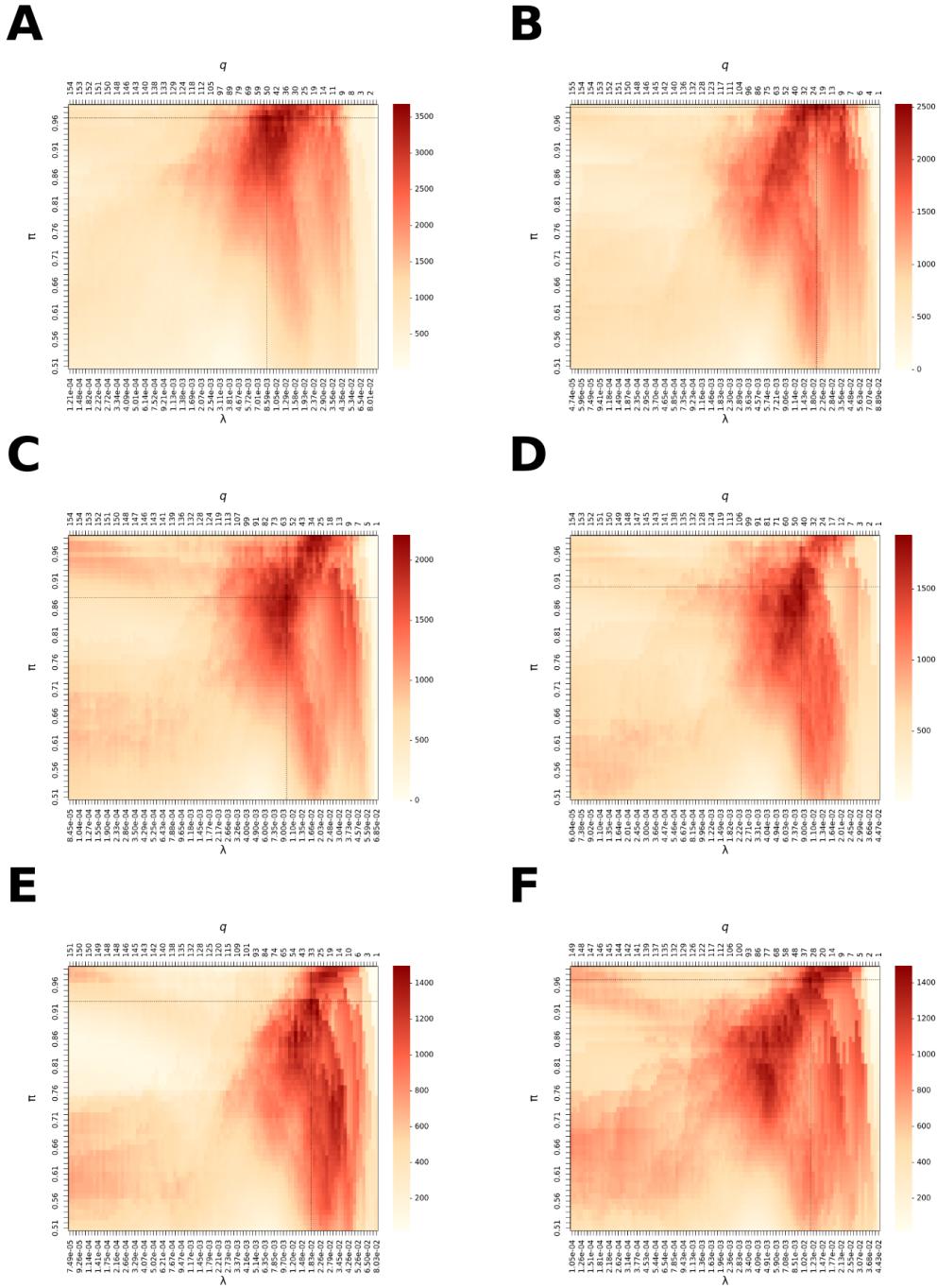
**Fig. 1** Workflow of Gender-Stratified Analyses Data Preparation: Including Train-Test Split, MissForest Imputation, One-Hot Encoding, and Removal of Biomarkers.

## S.2 Descriptive Analysis of Prescription Data

**Table 1** Summary of prescription metrics by sex and case/control status. Standard deviation is abbreviated as SD.

	Female			Male		
	Case (%)	Control (%)	Total	Case (%)	Control (%)	Total
<b>Overall</b>	4,225	12,675	16,900	2,730	8,190	10,920
<b>Number of prescriptions</b>						
0	0	11,680 (92.1)	11,680	0	7,712 (94.2)	7,712
1	0	846 (6.7)	846	0	426 (5.2)	426
2	1,252 (29.6)	123 (1.0)	1,375	929 (34.0)	43 (0.5)	972
3+	2,973 (70.4)	26 (0.2)	2,999	1,801 (66.0)	9 (0.1)	1,810
<b>BZD prescription</b>						
<b>Drug name</b>						
Diazepam	18,759 (51.3)	951 (80.8)	19,710	12,486 (46.3)	391 (72.6)	12,877
Temazepam	7,442 (20.3)	178 (15.1)	7,620	5,235 (19.4)	94 (17.4)	5,329
Clonazepam	5,070 (13.9)	9 (0.8)	5,079	5,330 (19.7)	5 (0.9)	5,335
Lorazepam	2,976 (8.1)	13 (1.1)	2,989	2,078 (7.7)	12 (2.2)	2,090
Others	2,343 (6.4)	26 (2.2)	2,369	1,872 (6.9)	37 (6.9)	1,909
<b>Total prescriptions</b>	36,590	1,177	37,767	27,001	539	27,540
<b>Average prescriptions (SD)</b>	8.66 (17.9)	0.09 (0.35)	2.23 (9.7)	9.89 (24.5)	0.07 (0.3)	2.52 (12.9)

### S.3 Stability Selection Calibration Plots



**Fig. 2** Stability selection calibration plots for logistic regressions conducted. Colour intensity indicates the stability score for a given combination of the penalty parameter  $\lambda$  and selection proportion  $\pi$ . Each logistic LASSO underwent calibration, with A) denoting the calibration plot for all females, B) for all males, C) for females with anxiety, D) for females without anxiety, E) for males with anxiety, and finally F) for males without anxiety.

## S.4 Decision tree parameters

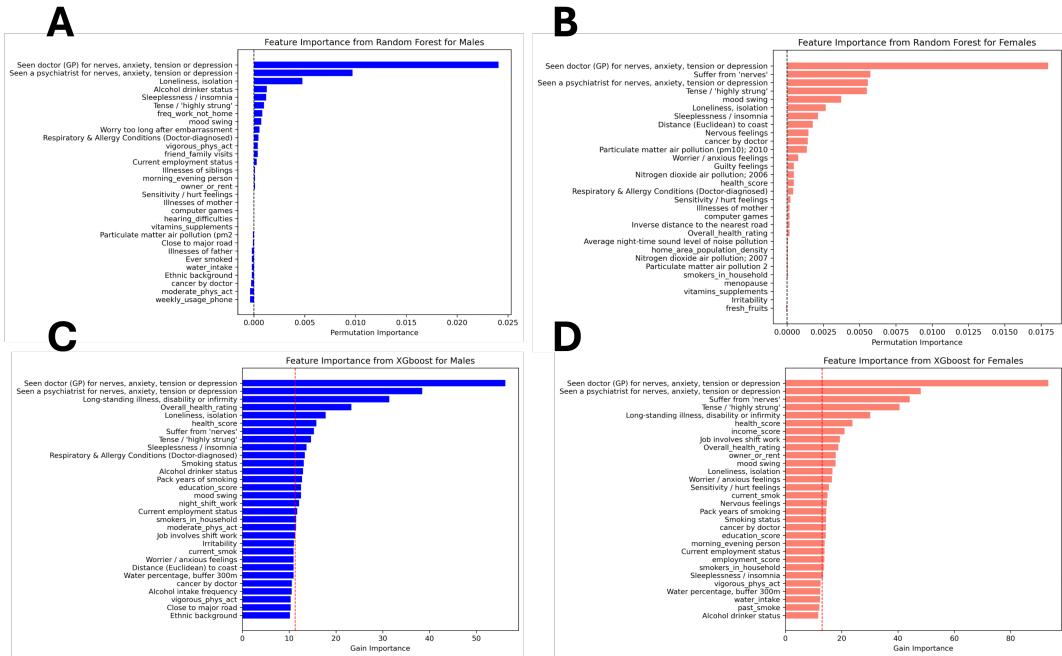
Parameters	Grid	Male/Female	Female Anxious/Non-Anxious	Male Anxious/Non-Anxious	Biomarkers Male/Female
Nb estimators	[500, 1000, 1250]	500 / 1250	1000 / 1250	1250	1250 / 1000
Criterion	"Gini", "Entropy"	"Gini"	"Gini"	"Gini"	"Gini"
Max Depth	Range(3,8)	7	7	7	8
Min Sample Split	Range(2,5)	2	2	2	2
Min Sample Leaf	[5, 10, 15]	15 / 10	5	5	3
Max Features	"Sqrt", "Log2", "0.3", "0.5"	"Sqrt" / "Log2"	"Log2"	"Log2"	"0.5" / "0.3"

**Table 2** Hyperparameter grid for random forest.

Parameters	Grid	Male/Female
Nb estimators	[100, 500, 1000]	500
Subsamples	[0.5, 0.7, 0.9]	0.5
Max Depth	[3, 5, 7, 9]	3
Min Child Weight	[1, 3, 5]	5
Learning Rate	[0.01, 0.0575, 0.105, 0.1525, 0.2]	0.01
Gamma	[0, 0.1, 0.2, 0.3]	0.2
Colsample by Tree	[0.5, 0.7, 0.9]	0.7

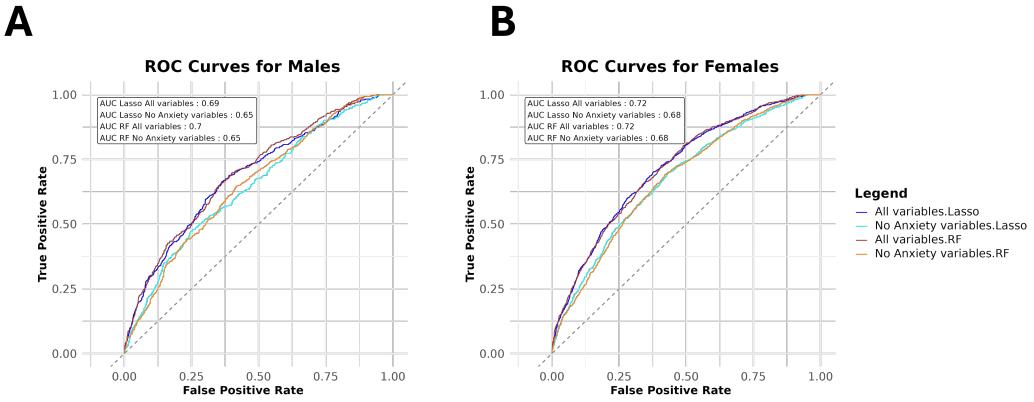
**Table 3** Hyperparameter grid for XGBoost.

## S.5 Variables Importance plots



**Fig. 3** Cropped Variable importance plot for the selection of variables: A) Positive Permutation variable for males for random forest, B) Positive Permutation variable for females for random forest, C) Gain value for males for XGBoost, D) Gain value for females for XGBoost. The red dashed lines in XGBoost plots represent the 3<sup>rd</sup> quartile of all the gains.

## S.6 ROC Curves of anxiety variables removed analysis



**Fig. 4** ROC curves split by sex (A males and B females) with (i) all the predictors and (ii) without anxiety-related variables, using LASSO and random forest

## S.7 Logistic Regression Results Utilising Stably Selected Features.

Below are the results of a series of logistic regressions that utilise stably selected features as covariates, as chosen by the stability selection calibration procedure. Logistic regressions were conducted on study subpopulations stratified by biological sex and anxiety status.

**Table 4** Results from logistic regression investigating the effect of stably selected features on long-term BZD prescription in anxious males, including odds ratio (95% confidence interval) and associated p-values.

Variable	Odds Ratio	95% CI	p-value
(Intercept)	0.746	0.478, 1.160	0.194
Suffer from nerves (Yes)	1.270	0.916, 1.760	0.150
Loneliness/isolation (No)	0.842	0.584, 1.220	0.357
Long-standing illness/disability/infirmity (No)	0.620	0.439, 0.876	0.007
Current employment status (Employed)	0.808	0.580, 1.130	0.208
Health score	0.329	0.155, 0.590	0.001
Overall health rating: Poor	1.830	1.090, 3.110	0.022

**Table 5** Results from logistic regression investigating the effect of stably selected features on long-term BZD prescription in non-anxious males, including odds ratio (95% confidence interval) and associated p-values.

Variable	Odds Ratio	95% CI	p-value
(Intercept)	0.257	0.190, 0.341	< 0.001
Long-standing illness/disability/infirmity (No)	0.628	0.467, 0.848	0.002
Pack years of smoking	1.060	0.927, 1.220	0.368
Health score	0.373	0.181, 0.644	0.003
Overall health rating: Poor	1.250	0.653, 2.310	0.480
Overall health rating: Fair	1.120	0.796, 1.560	0.507

**Table 6** Results from logistic regression investigating the effect of stably selected features on long-term BZD prescription in anxious females, including odds ratio (95% confidence interval) and associated p-values.

Variable	Odds Ratio	95% CI	p-value
(Intercept)	0.260	0.171, 0.392	< 0.001
Weekly phone usage: 30–59 mins	0.985	0.728, 1.330	0.922
Morning person	0.964	0.772, 1.200	0.746
Insomnia (Yes)	1.200	0.870, 1.660	0.274
Water intake	1.040	0.937, 1.160	0.433
Hurt feelings (No)	1.150	0.886, 1.480	0.298
Tense/highly strung (Yes)	1.330	1.030, 1.730	0.031
Suffer from nerves (Yes)	1.640	1.280, 2.120	< 0.001
Long-standing illness/disability (Yes)	1.520	1.210, 1.900	< 0.001
Cancer diagnosed (Yes)	1.380	0.946, 2.010	0.093
Employment status: Employed	0.976	0.782, 1.220	0.834
Income score	1.410	1.230, 1.620	< 0.001
Health score	0.248	0.143, 0.394	< 0.001
Overall health rating: Excellent	0.728	0.492, 1.060	0.106

**Table 7** Results from logistic regression investigating the effect of stably selected features on long-term BZD prescription in non-anxious females, including odds ratio (95% confidence interval) and associated p-values.

Variable	Odds Ratio	95% CI	p-value
(Intercept)	0.162	0.108, 0.237	< 0.001
Rents home	1.080	0.563, 1.970	0.803
Water intake	1.030	0.896, 1.170	0.695
Not tense/highly strung	0.673	0.464, 0.994	0.041
Long-standing illness/disability (Yes)	2.350	1.760, 3.120	< 0.001
Cancer diagnosed (Yes)	1.460	0.951, 2.180	0.075
Income score	1.130	0.940, 1.360	0.175
Health score	0.353	0.175, 0.603	0.001
Housing score	1.050	0.919, 1.200	0.455
Overall health rating: Fair	1.160	0.813, 1.630	0.406

## S.8 Variables Used for General Analysis

**Table 8:** Non-Biomarker Variables by Type

Variable Type	Variable Name
<b>Demographic Variables</b>	
	home owner or rent
	frequency of working away from home
	job involves heavy manual or physical work
	job involves shift work
	night shift work
	current employment status
	area population density
	ethnic background
	crime score
	living environment score
	income score
	employment score
	health score
	education score
	housing score
	Index of Multiple Deprivation (IMD) score
	age
<b>Lifestyle Variables</b>	
	moderate physical activity
	vigorous physical activity
	time spent watching television
	time spent using computer
	weekly phone usage
	morning/evening person (chronotype)
	sleeplessness or insomnia
	currently smokes
	smoked in the past
	smokers in household
	fresh fruit intake
	water intake
	alcohol intake frequency
	plays computer games
	smoking status
	alcohol drinker status
	ever smoked
	pack years of smoking

Variable Type	Variable Name
<b>Anxiety Related Variables</b>	
	visits from friends or family
	mood swings
	irritability
	sensitivity or hurt feelings
	nervous feelings
	worrier or anxious feelings
	feeling tense or highly strung
	worry too long after embarrassment
	suffers from nerves
	loneliness or social isolation
	guilty feelings
	seen GP for anxiety, tension or depression
	seen psychiatrist for anxiety, tension or depression
<b>Clinical Variables</b>	
	long-standing illness, disability or infirmity
	hearing difficulties
	cancer diagnosis by doctor
	respiratory or allergic illness diagnosed by doctor
	use of vitamins or supplements
	father's illnesses
	mother's illnesses
	siblings' illnesses
	forced vital capacity (FVC), best measure
	predicted FEV1
	body mass index (BMI)
	weight
	overall health rating
<b>Environment Related Variables</b>	
	nitrogen dioxide air pollution (2010)
	nitrogen oxides air pollution (2010)
	PM10 air pollution (2010)
	PM2.5 air pollution (2010)
	PM2.5 absorbance (2010)
	PM 2.5–10 µm air pollution (2010)
	inverse distance to nearest road
	inverse distance to major road
	close to major road
	sum of road length within 100m
	nitrogen dioxide air pollution (2005)

Variable Type	Variable Name
	nitrogen dioxide air pollution (2006)
	nitrogen dioxide air pollution (2007)
	PM10 air pollution (2007)
	average daytime noise level
	average evening noise level
	average night-time noise level
	greenspace percentage (1000m buffer)
	domestic garden percentage (1000m buffer)
	water percentage (1000m buffer)
	greenspace percentage (300m buffer)
	domestic garden percentage (300m buffer)
	water percentage (300m buffer)
	natural environment percentage (1000m buffer)
	natural environment percentage (300m buffer)
	distance to coast (Euclidean)
<b>Sex-related Variables</b>	
	menopause status
	use of contraceptive pill

## S.9 Variables Used for Biomarker Analysis

**Table 9:** Biomarkers by Type

Biomarker Type	Biomarker Name
<b>Lipids &amp; Lipoproteins</b>	
	Total Cholesterol
	Total Cholesterol Minus HDL-C
	Remnant Cholesterol (Non-HDL, Non-LDL)
	VLDL Cholesterol
	Clinical LDL Cholesterol
	LDL Cholesterol
	HDL Cholesterol
	Total Triglycerides
	Triglycerides in VLDL
	Triglycerides in LDL
	Triglycerides in HDL
	Total Phospholipids in Lipoprotein Particles
	Phospholipids in VLDL
	Phospholipids in LDL
	Phospholipids in HDL
	Total Esterified Cholesterol
	Cholesteryl Esters in VLDL
	Cholesteryl Esters in LDL
	Cholesteryl Esters in HDL
	Total Free Cholesterol
	Free Cholesterol in VLDL
	Free Cholesterol in LDL
	Free Cholesterol in HDL
	Total Lipids in Lipoprotein Particles
	Total Lipids in VLDL
	Total Lipids in LDL
	Total Lipids in HDL
	Total Concentration of Lipoprotein Particles
	Concentration of VLDL Particles
	Concentration of LDL Particles
	Concentration of HDL Particles
	Average Diameter for VLDL Particles
	Average Diameter for LDL Particles
	Average Diameter for HDL Particles
<b>Fatty Acids</b>	
	Phosphoglycerides

Biomarker Type	Biomarker Name
	Triglycerides to Phosphoglycerides ratio
	Total Cholines
	Phosphatidylcholines
	Sphingomyelins
	Total Fatty Acids
	Degree of Unsaturation
	Omega-3 Fatty Acids
	Omega-6 Fatty Acids
	Polyunsaturated Fatty Acids
	Monounsaturated Fatty Acids
	Saturated Fatty Acids
	Linoleic Acid
	Docosahexaenoic Acid
	Omega-3 Fatty Acids to Total Fatty Acids percentage
	Omega-6 Fatty Acids to Total Fatty Acids percentage
	Polyunsaturated Fatty Acids to Total Fatty Acids percentage
	Monounsaturated Fatty Acids to Total Fatty Acids percentage
	Saturated Fatty Acids to Total Fatty Acids percentage
	Linoleic Acid to Total Fatty Acids percentage
	Docosahexaenoic Acid to Total Fatty Acids percentage
	Polyunsaturated Fatty Acids to Monounsaturated Fatty Acids ratio
	Omega-6 Fatty Acids to Omega-3 Fatty Acids ratio
<b>Amino Acids</b>	
	Alanine
	Glutamine
	Glycine
	Histidine
	Total Concentration of Branched-Chain Amino Acids (Leucine + Isoleucine + Valine)
	Isoleucine
	Leucine
	Valine
	Phenylalanine
	Tyrosine
<b>Glycolysis-related Metabolites</b>	
	Glucose
	Lactate
	Pyruvate

Biomarker Type	Biomarker Name
	Citrate
<b>Ketone Bodies</b>	
	3-Hydroxybutyrate
	Acetate
	Acetoacetate
	Acetone
<b>Inflammatory Markers &amp; Proteins</b>	
	Creatinine
	Albumin
	Glycoprotein Acetyls
	C-reactive protein
	Cystatin C
<b>Blood Cell Counts &amp; Indices</b>	
	White blood cell (leukocyte) count
	Red blood cell (erythrocyte) count
	Haemoglobin concentration
	Haematocrit percentage
	Mean corpuscular volume
	Mean corpuscular haemoglobin
	Red blood cell (erythrocyte) distribution width
	Platelet count
	Platelet crit
	Mean platelet (thrombocyte) volume
	Platelet distribution width
	Lymphocyte count
	Monocyte count
	Neutrophil count
	Eosinophil count
	Basophil count
	Nucleated red blood cell count
	Lymphocyte percentage
	Monocyte percentage
	Neutrophil percentage
	Eosinophil percentage
	Basophil percentage
	Nucleated red blood cell percentage
<b>Reticulocyte Measures</b>	
	Reticulocyte percentage
	Reticulocyte count

Biomarker Type	Biomarker Name
	Mean reticulocyte volume
	Mean spheroid cell volume
	Immature reticulocyte fraction
	High light scatter reticulocyte percentage
	High light scatter reticulocyte count
<b>Urinary Electrolytes</b>	
	Potassium in urine
	Sodium in urine
<b>Serum Biochemistry</b>	
	Albumin (2)
	Alkaline phosphatase
	Alanine aminotransferase
	Aspartate aminotransferase
	Direct bilirubin
	Urea
	Calcium
	Cholesterol
	Creatinine (2)
	Gamma glutamyltransferase
	Glucose (2)
	Glycated haemoglobin (HbA1c)
	HDL cholesterol (2)
	LDL direct
	Lipoprotein A
	Phosphate
	Total bilirubin
	Total protein
	Triglycerides
	Urate
	Estimated sample dilution factor
<b>Hormones</b>	
	Apolipoprotein A
	Apolipoprotein B (2)
	IGF-1
	SHBG
	Testosterone