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Clusters of personality traits and psychological symptoms associated with later benzodiazepine prescriptions in the general population: The HUNT Cohort Study

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Abstract

Objective: The aim of this population-based study was to identify factors associated with later benzodiazepine prescriptions, including clusters of personality traits, self-esteem characteristics, sleep difficulties, depression and anxiety symptoms.

Methods: A 13 year historical cohort study (n = 58 967) was carried out and baseline measures of self-reported depression and anxiety symptoms, sleep difficulties, self-esteem and personality traits were obtained from the second wave of the Nord-Trøndelag Health Study (HUNT 2, 1995-1997), Norway. Data on benzodiazepine prescriptions were collected from the Norwegian Prescription Database (NorPD, 2004-2008) for each case in the cohort.

Results and Conclusions: We found that a combined high extraversion and high neuroticism personality score at baseline was associated with increased benzodiazepine prescription rates. Further, sleep difficulties, low self-esteem and high depression and anxiety scores were also linked to later prescriptions of benzodiazepines, in particular chronic and high dose benzodiazepine prescriptions patterns. The findings are discussed in relation to prescription practice and policy.

KEY WORDS: Personality; depression; anxiety; self-esteem; sleep; benzodiazepine

Benzodiazepines (BZ) are among the most commonly prescribed classes of medications for the treatment of anxiety symptoms (Ashton, 2005) and sleep problems (Sivertsen et al., 2010). Population studies have demonstrated prescription prevalence rates in the range of 3% to 17% in different countries, depending upon the follow-up period (Cunningham et al., 2010; Fang et al., 2009; Magrini et al., 1996). Estimates show that approximately 6% of Norwegians received at least one prescription of BZ in the period 2004-2009, with an annual incidence rate of approximately 2% (Bramness & Sexton, 2011).

BZ exert sedative and anxiolytic effects as agonists at gamma-aminobutyric acid neurotransmitter ($GABA_A$) receptors. International clinical practice guidelines vary according to their recommendation for the short term use of BZ for anxiety treatment (American Psychiatric Association, 2009; National Institute for Health and Clinical Excellence, 2007), however all agree such treatment is not appropriate over the long term (>1 month). The risk benefit ratio of long term use of these medications is far less favorable, as they have addictive potential and may cause substantial withdrawal symptoms (Fang et al., 2009). In sum, the unfavorable side effects, consequences and poor outcomes of BZ use are well-documented including cognitive decline (Buffett-Jerrott et al., 2002), increased risk of falls and fracture (Sylvestre et al., 2011), disturbed sleep and increased anxiety (Nordfjærn, 2012), muscular tension, fibrillations and uncomfortable bodily sensations (Longo & Johnson, 2000).

Although psychological symptoms like anxiety and insomnia are common indications for BZ prescription (Fang et al., 2009; Hausken et al., 2010; Isacson, 1997), few long-term prospective studies have examined the role of other factors associated with BZ prescriptions such as personality traits and other enduring psychological traits in combination with state psychological symptoms. A cross-sectional study of 118 BZ users found that neuroticism and

introversion were related to long-term use (Nicholas & Hammond, 1992). Short-term prospective studies have demonstrated that people with combined high neuroticism and introversion report stronger withdrawal symptoms during BZ discontinuation than individuals with low scores on these personality traits (O'Connor et al., 2004; Schweizer et al., 1998).

However, the predisposing role of personality traits in regards to later BZ use is unclear as even some cross-sectional studies reported relatively weak associations between personality traits and BZ use (Dåderman & Edman, 2001; Manthey et al., 2011). Previous studies examining sleep difficulties, diminished self-esteem, depression and anxiety symptoms related to future BZ use report contradictory findings (Brunette et al., 2003; Hausken et al., 2010; Jorm et al., 2000). Intriguingly, although temporal states (e.g. symptoms of depression, anxiety and sleep difficulties) and more stable personality traits overlap considerably, their relation to BZ use has often been studied separately. Further, common limitations of previous studies were relatively small clinical samples not reflecting the general population, cross-sectional design, and self-report of BZ use. Small sample sizes have limited many studies to dichotomous classification of BZ use (i.e. use/no use or short- term/long-term use) instead of categorizations that take both frequency and dose of prescriptions into account.

We are not familiar with any study using cluster analysis of personality traits and other psychological markers to group individuals and examine later differences in BZ prescriptions. Cluster analysis allows for the examination of the combination of different psychological traits and symptoms, which could be used to obtain more specific descriptions of factors prospectively associated with receiving prescribed BZ.

The primary aim of this study was to identify associations between baseline clusters of personality traits, self-esteem, sleep difficulties and depression and anxiety symptoms with BZ prescriptions after 7-13 years. Because cluster analysis is mainly driven by empirical data, hypotheses regarding the associations were articulated after the cluster solutions were established.

2 Methods

2.1. Study setting and design

The second wave (1995-1997) of the Nord-Trøndelag Health Study in Norway (HUNT 2, http://www.ntnu.no/hunt/english) provided baseline data from the study cohort. This epidemiological study is one of the largest health investigations ever performed in a general population. All inhabitants aged 20 years and above residing in Nord-Trøndelag County (n = 92 100) were invited to a clinical health screening. A total of 65 648 individuals (71%) attended and completed a questionnaire (Holmen et al., 2003; http://www.ntnu.edu/hunt/data/que). The questionnaire data from this epidemiological survey were used to establish a unique link to individual prescriptions of BZ in the Norwegian Prescription Database (NorPD 2004 – 2008). The data were linked by the Norwegian Institute of Public Health and the HUNT Research Centre.

A historical cohort study design was deployed to examine the associations between personality traits, self-esteem and symptom load clusters assessed at HUNT 2 in 1995-1997 (baseline), with later BZ prescriptions obtained from the NorPD between 2004 and 2008. Because demographics and previous use of psychopharmacological agents may be associated with later BZ, these variables were adjusted for in the analysis. The Anatomical Therapeutic Chemical Classification System (ATC) was used to identify BZ in the NorPD (anxiolytics

code N05B and hypnotics code N05CD). There is no formal standard of defining frequency patterns of BZ prescriptions. In the present study a single period prescription was defined as receiving one prescription in the period 2004-2008. Intermittent prescriptions were defined as receiving prescriptions in two or more years, but with a pause of at least one year during the 4-year period. Chronic prescriptions were defined as receiving prescriptions for two or more consecutive years without any pause (Hartz et al., 2011; Madhusoodanan & Bogunovic, 2004). Defined Daily Doses (DDD) (WHO, 2011) may be a more robust indicator of the extent and appropriateness of BZ use than prescription frequencies. Therefore, we also applied this measure in the analyses. The DDD is based on statistics and clinical practice with a wide range of medications and constitutes the assumed average maintenance dose per day for a drug used for its main indication in adults. Based on the WHO standard and previous research (Fang et al., 2009; Hartz et al., 2011) a total DDD above 180 on a yearly basis was defined as high BZ dose prescriptions.

2.2. Ethical considerations

All HUNT participants gave their informed written consent, which could be withdrawn at any time after HUNT 2. The protocols of the present study as well as HUNT 2 and HUNT 3 were approved by the Regional Committee for Ethics in Medical Research, The Norwegian Data Inspectorate as well as the HUNT Publication Board and the Norwegian Institute of Public Health Board.

2.3. Baseline assessment

Baseline (HUNT 2) anxiety and depression symptoms were recorded by the 14-item Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The instrument was scored on a 0-3 Likert scale.

The instrument is widely used in various health care and research settings (Berk et al., 2011) and has demonstrated a consistent two-factor structure related to anxiety (HADS-A) and depression (HADS-D) symptoms (Stafford et al., 2007). The sub-scales were found to have acceptable validity and reliability characteristics across 15 studies with Cronbach's alphas for the HADS-A ranging from .68 to .93 and .67 to .90 for the HADS-D (Bjelland et al., 2002). The same study found that with a cut-off score at 8 or above both sub-scales had sensitivity and specificity around .80. Consequently, this cut-off score was also applied in the present study.

Sleep difficulties were measured by the following four items at baseline: 'How often do you suffer from sleeplessness' (never or a few times a year; 1-2 times a month; approximately once a week; more than once a week), 'Have you the last year suffered by sleeplessness to the extent where it influenced your work capability' (yes/no), 'Have you experienced difficulties to fall asleep the last month' (never; sometimes; often; almost each night) and 'During the last month have you woke up prematurely and not been able to regain sleep' (never; sometimes; often; almost each night). A sleep difficulty index was calculated on the basis of the responses with higher scores reflecting more sleep difficulties.

A revised six-item version of the Rosenberg (1965) 10-item Self-esteem Scale was included at baseline (Grayson, 1986). This instrument has good psychometric properties (Rosenberg, 1989). Personality traits were measured by a short version of the Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975). The instrument has been shown to consist of two 6-item dimensions: neuroticism and extraversion (Francis et al., 2006). The items are scored by yes/no responses to questions such as 'Can you get a party going' and 'Are your

feelings easily hurt'. Grayson (1986) reported similar psychometric qualities across the short and long forms of the EPQ.

Because the Norwegian Prescription Database (NorPD) was established in 2004, we also included some self-reported demographic and pharmacological baseline control variables. Use of medications at baseline contained items about the intake of one or more of the following medications: "antidepressants", "tranquillisers", and "sleep medication". A positive response to one or more of these items was defined as use of psychotropic drug use at baseline. Rikala et al. (2010) compared self-reported medication use with pharmacy records and found that the sensitivity of self-report use of psychotropic drugs tend to vary across different subcategories (0.57-0.96). The specificity was generally found to be high across sub-groups of medications (0.94-0.99), but declined slightly over time. Information about demographic characteristics was also collected, including gender, age, and levels of completed education.

2.4. Statistical analysis

Descriptive statistics were used to describe baseline characteristics of the study cohort. Two hierarchical cluster analyses were then carried out to identify the optimal number of clusters for z-scores on the personality traits, self-esteem and symptom load measures. The distance between the coefficients was investigated to find a marked increase in the coefficients and the optimal number of clusters was set to the gap before the sudden increase (Aldenderfer & Blashfield, 1984). The dendrogram was also visually inspected to determine the optimal cluster solution. Hierarchical cluster analysis is not capable of producing the most optimal cluster solution in regards to between-cluster heterogeneity. Therefore, the hierarchical cluster analysis was followed by an iterative partitioning method (*k* – means) to identify the optimal

cluster solution. The *k*-means cluster analysis allocates each case to the cluster that has the nearest centre point. When all the respondents had been sorted the final cluster solution was achieved. A multinomial logistic regression analysis was performed to test whether cluster belongingness was associated with later patterns of BZ prescriptions (single period, intermittent and chronic prescriptions). Non-BZ prescription was the reference category. A logistic regression analysis was used to investigate whether the clusters related to later dose prescriptions (low dose/high dose). Pseudo R-squared (Nagelkerke R^2 and Cox & Snell R^2) together with the -2 Log likelihood were estimated for the multinomial and binary logistic regression analyses. Due to the large sample size a conservative alpha level of .001 was used in all statistical analyses. All analyses were conducted with PASW Statistics 18.

3. Results

3.1. Cohort characteristics

The demographic characteristics, general health and BZ prescriptions in the present cohort have been reported in detail elsewhere (Nordfjærn, 2012). There were 54% females and 46% males in the cohort and the average age was 50.79 years (SD = 19.71, range = 20-103 years). The majority (78%) of the cohort had basic education (i.e. elementary school + high school), while 22% had a higher education from university/college. A total of 17% (n = 9 735) had received at least one prescription of BZ in the study period. Among these individuals, the majority received Oxazepam (48%) or Diazepam (36%). Fewer individuals received Nitrazepam (9%) and Clonazepam (4%), whereas Alprazolam (.33%), Flunitrazepam (2%) and Midazolam (.67%) were the least commonly prescribed BZ in the sample. Among the 9735 who received a BZ prescription in the study cohort, 36% had a single period prescription, 22% intermittent prescriptions and 42% chronic prescriptions. A total of 18%

were categorized as receiving high dose BZ prescriptions and the remaining 82% reflected low dose prescriptions.

3.2. Cluster solutions for personality traits, self-esteem, sleep difficulties and symptoms of anxiety and depression

Hierarchical cluster analysis identified four clusters for z-scores of personality traits, and three clusters for z-scores of self-esteem, depression and anxiety symptoms and sleep difficulties (Table 1). The *k*-means cluster analysis for personality traits showed that Personality cluster 1 (15%) consisted of individuals who reported low extraversion and high neuroticism. People in this cluster are likely to be relatively introverted and shy, as well as prone to negative emotions and to be highly reactive to stressors. This group was hypothesized to be at higher risk for receiving BZ. Personality cluster 2 (43%) contained individuals who reported a high extraverted personality style coupled with low neuroticism. These individuals are likely to be relatively assertive, social and outgoing, while being relatively resilient when exposed to stressors and demanding situations. This group was expected to be less likely to receive BZ. Personality cluster 3 (28%) contained people with relatively low extraversion and neuroticism. Individuals belonging to this cluster could be expected to be relatively calm and shy, but emotionally stable, and as such be at low risk in terms of BZ prescriptions. People in personality cluster 4 (14%) contained individuals who reported high scores on both extraversion and neuroticism. Individuals in this cluster may be aroused and assertive, while being prone to negative emotions and stress. These individuals may be biologically aroused, but their high extraversion may moderate their risk of receiving prescribed BZ.

The *k*-means cluster analysis showed that people in symptom cluster 1 (50%) reported few sleeping difficulties, relatively high self-esteem and few symptoms of anxiety and depression.

This group may not be substantially exposed to risk factors of BZ prescriptions and could be relatively resilient to stressors due to their higher self-esteem. Individuals belonging to symptom cluster 2 (36%) reported moderate sleep difficulties, self-esteem and symptoms of depression and anxiety. This is a relatively vague cluster, as people in this cluster do not diverge in any specific direction on the psychological factors. Based on their scores it was, however, expected that this group would have a somewhat higher risk of BZ prescriptions than people in symptom cluster 1. Symptom cluster 3 (15%) contained individuals who reported high sleep difficulties, depression and anxiety symptoms coupled with low self-esteem. This group could be expected to be at risk of receiving BZ prescriptions.

Insert Table 1 about here

3.3. Relations between personality traits, self-esteem and psychological symptom clusters and later BZ prescriptions

As seen in Table 2, the multinomial model showed satisfactory fit to the data (-2 Log likelihood = 3.06, $\chi^2 = 5.49$, df = 30, $p < .001$) and explained a satisfactory proportion of variance in BZ prescription patterns as reflected by the pseudo R^2 estimations (Nagelkerke R^2 = .23, Cox & Snell R^2 = .19). While adjusting for demographic variables and use of psychopharmacological agents at baseline, the results showed that people with a combined high extraversion and high neuroticism (personality cluster 4) constituted a specific risk group for all patterns of BZ prescriptions. Individuals in the cluster reporting low extraversion and low neuroticism (personality cluster 3) had a substantially reduced risk of using prescribed BZ and the protective role of this personality type combination increased systematically by

more frequent patterns of BZ prescriptions. There were no differences in the risk of receiving prescribed BZ between people in the cluster reporting low extraversion and high neuroticism (personality cluster 1) and those in the cluster with high scores on both personality traits (personality cluster 4).

Individuals belonging to the cluster reporting high sleep difficulties, low self-esteem and high depression and anxiety symptoms (symptom cluster 3) constituted a high risk group for all patterns of BZ prescriptions and, in particular, chronic prescriptions. Belonging to the cluster that reported low sleep difficulties, high self-esteem coupled with low depression and anxiety symptoms (symptom cluster 1) was associated with a reduced risk of later prescribed BZ. This tendency increased by more frequent BZ prescription patterns. However, moderate levels of sleep difficulties, depression and anxiety symptoms, and self-esteem (symptom cluster 2) were also associated with a reduced risk of BZ prescriptions compared to the reference category. This tendency increased by more frequent BZ prescription patterns.

Insert Table 2 about here

A binary logistic regression analysis with BZ doses (low/high) as the dependent variable and the same predictors as above showed good fit to the data (-2 Log likelihood = 2.64, $\chi^2 = 2.38$, df = 5, $p < .001$). The model also explained a satisfactory amount of the variance in BZ dose prescriptions (Nagelkerke $R^2 = .17$; Cox & Snell $R^2 = .12$). The analysis showed that people with a combined high extraversion and high neuroticism (personality cluster 4) constituted a high risk group for high dose prescriptions of BZ. People in the cluster with low extraversion

and low neuroticism (personality cluster 3), had the lowest risk of high dose BZ prescriptions (OR = .62, CI 95% = .52; 74). Individuals with high extroversion and low neuroticism (personality cluster 2) did also have a reduced risk of high dose BZ prescriptions (OR = .65, CI 95% = .54; 79). There were no significant differences in the risk of high dose prescriptions between the cluster with low extraversion and high neuroticism (personality cluster 1), and the cluster with high scores on both personality traits (personality cluster 4).

Individuals who belonged to the cluster reporting high symptoms of anxiety and depression and sleep difficulties as well as low self-esteem (symptom cluster 3), had an increased risk of receiving high doses of BZ. People with high self-esteem and low symptom load (symptom cluster 1) (OR = .46, CI 95% = .39; 55) and individuals with moderate scores on these variables (symptom cluster 2) (OR = .42, CI 95% = .36; .50), had a lower risk of high dose BZ prescriptions compared to the category of reference.

4. Discussion

Results from this large population-based study indicate that different clusters of personality traits and psychological symptoms (sleep difficulties, depression and anxiety symptoms and diminished self-esteem) are differentially associated with later BZ prescriptions, in terms of both prescription patterns and dosage.

In our study, combined high extraversion and high neuroticism (personality cluster 4) appeared as a high risk profile regarding later prescriptions of BZ, both in terms of more frequent prescriptions and doses exceeding international clinical recommendations (WHO, 2011). As hypothesized, low extraversion and high neuroticism (personality cluster 1) was a personality type combination at risk for BZ prescriptions, whereas high extraversion and low neuroticism (personality cluster 2) and, in particular, low scores on both traits (personality cluster 3) related to a reduced probability of later frequent and high dose prescriptions.

As hypothesized, individuals who belonged to the cluster reporting high sleep difficulties and high depression and anxiety symptoms coupled with low self-esteem (symptom cluster 3) had a higher probability of later frequent and high dose BZ prescriptions. Although the opposite was true for individuals reporting low depressive and anxiety symptoms, sleep difficulties and high self-esteem (symptom cluster 1), an additional protective combination was moderate depressive and anxiety symptoms, sleep burden and self-esteem (symptom cluster 2). This group did not differentiate substantially in BZ prescriptions compared to people with low depressive and anxiety symptom loads and high self-esteem.

Previous work suggests that people with low extraversion and high neuroticism are at highest risk for later BZ prescriptions (e.g. O'Connor et al., 2004; Manthey et al., 2011; Nicholas &

Hammond, 1992). These results are in contrast with our findings, and we can think of several possible explanations for this discrepancy. Intriguingly, the protective role of extraversion was described in cross-sectional studies (Manthey et al., 2011; Nicholas & Hammond, 1992), where causal relations cannot be inferred. In the long term, high conscientiousness may increase stress levels in extraverted individuals and cause autonomous arousal, anxiety and sleep difficulties. Recent studies have supported this assumption by demonstrating that extraverted individuals have high activation in the right insular cortex, which in turn affect motoric control and biological homeostasis (Kehoe et al.,2012).. Extraversion alone may reduce the risk of later BZ prescriptions, but the present findings based on cluster analysis suggest that extraversion solely relate to a reduced probability of later BZ prescriptions in the absence of high neuroticism. In this regard, extraverted people with neuroticism may display different sickness behaviours, seeking help from caregivers and therefore gaining access to drug treatment more readily than introverted individuals. There is good evidence from this HUNT 2 cohort (Roness et al., 2005) and from a variety of medical settings that symptoms of depression is associated with lower help-seeking compared to anxiety (Simon et al., 1995) and mixed anxiety and depression (Roy-Byrne et al., 2000).

The cortical arousal theory (Eysenck, 1967) could also shed light on the present findings. The theory argues that people have an optimal stage of cortical arousal and that psychological functioning may be reduced when the arousal deviates substantially from the optimal stage. People who report high extraversion and neuroticism could experience substantial arousal as they are likely to be restless, obsessive, impulsive and anxious. Individuals who report relatively low scores on both traits are likely to be less outgoing and shyer than individuals with high extraversion and neuroticism. In contrast, they may also reflect more emotional and biological stability (Kehoe et al., 2012) which could make them less prone to receive BZ

prescriptions. This personality combination was found to be at the lowest risk of later BZ prescriptions in the present study, which was somewhat surprising compared to previous findings (Manthey et al., 2011; O'Connor et al., 2004).

An alternative interpretation, however, is that extraversion was operationalized differently across studies. Manthey et al. (2011) applied the NEO inventory, which assesses extraversion across six facets. Two of these facets, i.e. positive emotions and warmth, may be particularly likely to mitigate the effects of neuroticism. Nicholas (1992) used the long version of the EPQ that assessed these two facets. Neither positive emotions nor warmth are tapped by the items on the modified Eysenck EPQ, which was applied in the present study. Future studies should include the long version of the EPQ or apply the NEO inventory in order to investigate whether these two additional facets of extraversion are protective components of prescribed anxiolytic medications.

As hypothesized, people with sleep difficulties and high depression and anxiety symptoms coupled with low self-esteem were more likely to receive prescribed BZ, which is consistent with previous studies (Fang et al., 2009; Hausken et al., 2010). Our findings showed that the high symptom group received prescribed benzodiazepines at higher rates and higher doses than international clinical guidelines recommendation for treatment (American Psychiatric Association, 2009; National Institute for Health and Clinical Excellence, 2007). Our study also demonstrated that individuals with moderate psychological symptoms and moderate self-esteem did not differ substantially from people with low symptom load and high self-esteem in the risk of later BZ prescriptions. This could suggest that practitioners are more reluctant to prescribe these agents, or tend to recommend short term BZ treatment or other drug treatments (e.g. SSRIs) in individuals with mild and moderate psychological symptoms.

On a more general note, it is of concern that 42% of those who received BZ in the present cohort had a chronic prescription pattern, and that 18% had high dose prescriptions exceeding clinical recommendations. International clinical guidelines do not recommend BZ use beyond 2-4 weeks for most psychological diagnoses (National Institute for Health and Clinical Excellence, 2007) and dose use with DDD above 180 days is generally considered inappropriate (WHO, 2011). There are several efficient psychosocial treatment alternatives (e.g. exposure therapy and cognitive-behavioural therapy) for psychological issues related to anxiety and sleep difficulties (Espie, 2009; Stanley et al., 2003).

4.1. Strengths and Weaknesses

Strengths of the present study include a large cohort with a 13 year follow-up, analysis of cluster combinations of psychological constructs and both diverging prescription patterns and doses of BZ established by pharmacy records. Nevertheless, the study also has limitations that merit discussion. First, the study did not differentiate between long-acting and short-acting BZ. Such stratified analyses were not carried out because the vast majority of prescribed BZ in Norway is long acting medications, and stratified analyses may cause a type II error. Second, a potential weakness of the study is that we excluded Z-hypnotics from the analysis. These medications have largely replaced benzodiazepine prescriptions for minor sleep disorders (Mellingsæther et al., 2006). These medications were excluded in order to restrict the sample and the complexity of statistical analysis. Previous studies which focused on BZ also excluded the z-hypnotics from analysis (e.g. Bramness & Sexton, 2011; O'Connor et al., 2004). This may to some extent confound and weaken the associations between BZ use and sleep difficulties in the study, because people with less severe sleep difficulties are likely to be in the reference group. As such our findings may apply somewhat more to people with severe psychological symptoms. Third, we did not separate patients who received BZ due to

other indications than mental difficulties, such as epilepsy or neurological disorders. However, such disorders are relatively infrequent indications of BZ prescriptions and we do not believe that this has influenced the results. Finally, the study cohort was established between 1995 and 1997. Because registry data on drug prescriptions are solely available after 2004 in Norway, the drug prescription data were registered between 2004 and 2010. Hence, we do not know which drugs that were prescribed to the cohort between 1997 and 2004.

4.2. Conclusions & Future Directions

Our results indicate that individuals with different combinations of personality traits and state symptom clusters exhibit different rates of subsequent BZ prescriptions. Given that use of BZ for treatment of most psychological symptoms, particularly beyond the short term, is not supported by clinical practice guidelines, in combination with the knowledge that BZ are associated with a number of significant adverse effects, it is important to identify factors that may alter the probability of BZ prescription in the future. It is of great concern that about half of those who received BZ either had a chronic prescription pattern or received doses exceeding clinical recommendations. Our findings, however, indicate that a brief screening of personality traits and psychological symptom load could aid clinicians in detecting specific risk groups in the general population. These should be targeted by more conservative BZ prescription regimes and clear-cut discontinuations plans. Based on our results, there are also good reasons to believe that early and better tailored treatment of Axis I disorders including anxiety, depression and sleep disturbance might have potential in terms of preventing BZ treatment later in life. Future research into why different personality and symptom clusters confer different rates of subsequent BZ prescriptions, including into how these factors influence patient (e.g. rates of attendance) and doctor (e.g. attitudes towards individuals with differing personality traits) behaviours, would be of use.

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Table 1. Personality and symptom clusters in the study cohort

Personality clusters	Extroversion	Neuroticism	Symptom clusters	Sleep difficulties	Self-esteem	Anxiety	Depression
Personality cluster 1	Low	High	Symptom cluster 1	Low	High	Low	Low
Personality cluster 2	High	Low	Symptom cluster 2	Moderate	Moderate	Moderate	Moderate
Personality cluster 3	Low	Low	Symptom cluster 3	High	Low	High	High
Personality cluster 4	High	High					

Low, moderate and high scores defined on the basis of standardized z-scores (below, at or under the center-point of 0.00 at the z-scores, respectively)

Table 2. Associations between personality, symptom and self-esteem subtypes and later patterns of BZ prescriptions

Indicators	**Single period prescription**			**Intermittent prescriptions**			**Chronic prescriptions**		
	AOR	95% CI	*B*	AOR	95% CI	*B*	AOR	95% CI	*B*
H2 control variables									
Gender (female)	.68	.62-.75	**-.37**	.40	.35-.46	**-.92**	.43	.39-.48	**-.84**
Age	1.02	1.02-1.03	**.02**	1.05	1.05-1.06	**.05**	1.07	1.07-1.08	**.08**
Education (basic)	.92	.85-.97	-.09	1.05	.97-1.14	.05	.98	.92-.1.05	-.02
Baseline use of psychopharmacological agents (no)	1.31	1.19-1.45	**.27**	1.56	1.40-1.73	**.44**	2.28	2.07-2.52	**.83**
Cluster belongingness									
Personality cluster 1	.88	.75-1.04	-.13	.94	.79-1.13	-.06	.89	.77-.97	-.12
Personality cluster 2	.56	.49-.65	**-.54**	.42	.35-.49	**-.88**	.39	.34-.45	**-.94**
Personality cluster 3	.48	.41-.56	**-.73**	.32	.27-.39	**-1.13**	.31	.27-.36	**-1.17**
Personality cluster 4	-	-	-	-	-	-	-	-	-
Symptom cluster 1	.62	.54-.72	**-.48**	.44	.37-.52	**-.82**	.32	.28-.37	**-1.14**
Symptom cluster 2	.68	.59-.79	**-.38**	.50	.43-.48	**-.69**	.35	.31-.40	**-1.05**
Symptom cluster 3	-	-	-	-	-	-	-	-	-

-2 Log likelihood = 3.06, $\chi^2 = 5.49$, df = 30, $p < .001$, Nagelkerke $R^2 = .23$, Cox & Snell $R^2 = .19$

Reference dependent variable = non-BZ prescriptions

- = cluster reference group

B weights in bold are significant at $p < .001$ when controlling for all other factors in the model

AOR = Adjusted odds ratio

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Contributors

TN, OB, SM, MB and RWG designed the study and wrote the protocol. TN conducted the statistical analysis. TN wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Conflict of Interest

All other authors declare that they have no conflicts of interest.

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Highlights

- High extraversion and neuroticism traits related to increased BZ prescriptions
- State symptoms also related to BZ, especially chronic and high dose prescriptions
- Different trait and state clusters exhibit different rates of BZ prescriptions
- Screening of traits and state symptoms could aid in detecting risk groups

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