# Characterisation and Genetic Architecture of Major Depressive Disorder Subgroups Defined by Weight and Sleep Changes

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**Abstract**

Major depressive disorder is highly heterogeneous and is postulated to contain subgroups with different underlying aetiologies. The aim of this work is to further characterise depression subgroups defined using sleep and weight changes and investigate the effect of adjustment for BMI on results. Probable lifetime MDD cases (N = 26,662) from the UK Biobank were stratified into three subgroups defined by self-reported weight and sleep changes during worst episode: (i) increased weight and sleep (↑WS), (ii) decreased weight and sleep (↓WS) and (iii) the remaining individuals (non-↑↓WS). Analyses compared the depression characteristics, mental health scores, genetic architecture, and neurological and inflammatory comorbidities between subgroups and with 50,147 controls from UK Biobank. Sensitivity analyses compared results to those of subgroups defined by weight change only and analyses unadjusted for BMI. In contrast to ↑WS depression, ↓WS depression had a higher age of onset and lower proportion reporting countless or continuous episodes. The ↓WS depression subgroup also showed a higher wellbeing score compared to non-↑↓WS. Subgroup-specific GWAS identified three genome-wide significant loci associated with ↑WS in genes previously associated with obesity and response to anticonvulsants. In case-case subgroup comparisons, the ↑WS depression subgroup was significantly enriched for comorbid epilepsy, migraine and asthma, and there was significant variability in the odds ratios for dementia between subgroups. These findings provide further evidence for differences in the characteristics and genetic architecture of depression subgroups defined by sleep and weight change and highlight the importance of dividing non-↑WS individuals into ↓WS and non-↑↓ WS subgroups in analyses.

## Introduction

Major depressive disorder (MDD) is a polygenic and highly prevalent psychiatric disorder. In 2017 the World Health Organisation (WHO) estimated that there are around 322 million people living with depression globally, a figure that has grown 18.4% since 2005(1). Depression has a complex underlying genetic architecture, evidenced by the 178 risk loci identified in a recent meta-analysis of >1.2 million individuals(2). MDD is highly heterogeneous in presentation. For instance, using the criteria in the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V)(3), over 1,000 unique MDD diagnostic symptom profiles have been observed in a clinical setting(4). The variation in symptoms, severity and remission observed between individuals has resulted in the hypothesis that MDD includes multiple subgroups, with potentially different underlying aetiologies(5).

One proposed subgroup is MDD with atypical features, or 'atypical' depression, which is characterised in the DSM-V as MDD with any two of the following symptoms: mood reactivity, interpersonal rejection sensitivity, "leaden paralysis", weight gain, increased appetite, or hypersomnia(3). In particular, reversed neurovegetative symptoms (weight gain, increased appetite, and hypersomnia) have been observed to be highly specific to atypical depression(6). In contrast, weight loss, hypophagia and insomnia are frequently observed in 'typical' MDD patients. Thus, it is becoming increasingly common for both genetic(7-9) and epidemiological studies(10-12) to utilise these symptoms over the full DSM-V criteria when examining atypical depression. Epidemiological studies consistently show that individuals with atypical depression, are more likely to be female, have an earlier age of onset and have more frequent and more severe depressive episodes(13), than individuals with non-atypical depression, findings that have been replicated in the UK Biobank(12).

Atypical depression may be an immunometabolic subgroup of depression(14), as this subgroup has been associated with a number of inflammatory and metabolic traits(13). In the UK Biobank, individuals with atypical depression were shown have higher rates of obesity, cardiovascular disease and metabolic syndrome (hypertension, diabetes,

hypercholesterolemia) than those in a non-atypical depression group(12). There is also evidence to suggest there are differences in disease prevalence for migraine(15) and multiple sclerosis(16) between depression subgroups defined using neurovegetative symptoms. Genetic studies consistently show associations between atypical depression and polygenic risk scores (PRS) for body mass index (BMI)(7-9), triglycerides(7), leptin(8), C-reactive protein and daily alcohol use(9). Although, Nguyen *et al*. (2022) recently identified six loci associated ($p < 5 \times 10^{-8}$) with non-atypical depression in UK Biobank(17), no genome-wide significant loci associated with atypical depression have been identified to date. Identification of such loci may help to characterise this subgroup.

The estimated SNP heritability of atypical depression ranges from 0.11-0.43(7-9, 17), and the genetic correlation of atypical depression with other depression subgroups defined using weight and sleep changes ranges from 0.55-1.05(8, 9, 17). A potential explanation for the range of estimates observed for the SNP heritability and genetic correlation of atypical depression is that investigations thus far have utilised a variety of definitions for both depression and the neurovegetative subgroups. Some studies include individuals who self-report MDD(17), resulting in larger sample sizes. Others use only weight and appetite changes to define subgroups, as these have been shown to be highly discriminatory symptoms(7, 8). Frequently, atypical depression is compared only to a non-atypical group in main analyses combining ‘typical’ and unclassified individuals(12, 17). In some instances, these inconsistencies are unavoidable due to data constraints. For example, it is not possible to include information about appetite changes in investigations in the UK Biobank, as there is no question related to the direction of appetite change during worst depressive episode. Additionally, there is debate as to whether analyses should be corrected for BMI. Some perform correction on the basis that a significant difference in BMI is observed between subgroups(9). Whilst others argue that there is evidence for a shared genetic basis between atypical depression and BMI, and thus any correction may be an over

adjustment(7). Notably, studies of the genetic architecture of MDD overall do not correct for BMI in their analyses(2, 18-20).

The aims of this research were to: (i) further investigate the characteristics and overall genetic architecture of depression subgroups defined using weight and sleep and (ii) investigate the effect of utilising broader weight-only subgroup definitions and adjusting for BMI in genetic analyses.

## Materials and methods

### Participants

The samples were drawn from the UK Biobank. This cohort has been described in detail elsewhere(21) but briefly, the UK Biobank is a population-based study which includes over 500,000 genotyped and extensively phenotyped participants aged between 40-69 at recruitment. This research was conducted using the UK Biobank Resource—application number 4844. UK Biobank received ethical approval from the NHS National Research Ethics Service North West (reference: 11/NW/0382). All participants gave full informed written consent. 157,366 of UK Biobank participants have completed an online Mental Health Questionnaire (MHQ), based on the Composite International Diagnostic Interview Short Form (CIDI-SF), which aims to identify mental health conditions without an in person clinical assessment(22). Only unrelated individuals of genetically defined White British ancestry(19), that had completed the MHQ were included in these analyses (n = 122,639), participants in the Generation Scotland cohort and their relatives were also excluded.

### Genotyping and Quality Control (QC)

Genotyping of participants was performed using two arrays (the Applied Biosystems UK BiLEVE Axiom Array and the Applied Biosystems UK Biobank Axiom Array), which are highly overlapping and cover ~800,000 markers(23). Variants were excluded from analyses if they had a minor allele frequency (MAF) < 0.01, a high level of missingness (>0.05) or showed evidence of departure from Hardy-Weinberg equilibrium (HWE, $p < 1 \times 10^{-5}$). All genetic analyses were adjusted for technical covariates (array, batch and centre; UKB field 54 & UKB field 22000) as well as 40 genetic ancestry principal components (UKB field 22009), age, sex and, in the main analyses, BMI (UKB field 21001). There were some individuals for whom BMI was not available. Sample sizes for all analyses can be found in **Supplementary Table 1**.

## Phenotype Definitions

### *Probable Lifetime MDD*

Probable lifetime MDD cases (n = 26,662) were identified using the criteria outlined by Davis et al.(22). Briefly, these were individuals that reported depressed mood or anhedonia (or both) lasting longer than two weeks and impairing their daily life, as well as additional DSM-V MDD symptoms (at least four in total) during their worst depressive episode. Individuals with a psychotic, manic, personality or substance abuse disorder (recorded in electronic health records or self-reported to a trained nurse at baseline, in the touchscreen assessment or in the MHQ) were excluded in line with DSM-V criteria for depression(3). Further detail on the identification of individuals with probable lifetime MDD can be found in **Supplementary Figure 1**.

### *Depression Subgroups*

Depression subgroups were defined in line with previous studies of subgroups with reversed neurovegetative symptoms in the UK Biobank(9, 12). Individuals reporting increased weight (UKB field 20536) and sleeping more (UKB field 20534) during their worst episode were categorised as increased weight and sleep (↑WS, n = 1,525) representing atypical depression. Individuals reporting decreased weight (UKB field 20536) and sleeping less (UKB field 20533 or UKB field 20535) during their worst episode were categorised as decreased weight and sleep (↓WS, n = 9,076) representing typical depression. Individuals with lifetime MDD that did not fall into either subgroup were categorised as 'Non-Increased/Decreased Weight and Sleep' (non-↑↓WS, n = 16,070) (**Supplementary Figure 1**).

### *Controls*

Individuals that reported never having experienced a depressed mood and anhedonia for more than two weeks were classified as controls (UKB fields 20446 & 20441). Unlike in Davis *et* al.(22), individuals were not excluded from the control group based on patient

health questionnaire 9 (PHQ-9) score to avoid heavily screened so-called 'clean' controls, which can introduce bias to heritability estimates transformed to the liability scale(24, 25). Individuals with a depressive, psychotic, manic, personality or substance abuse disorder recorded in electronic health records (ICD10 codes, F05-07, F09, F10-39) or self-reported to a trained nurse at baseline (UKB field 20002), in the touchscreen assessment (UKB field 20126) or in the MHQ (UKB field 20544), were excluded from the control group.

**Mental Health Scores**

Four questionnaire-based scores relating to mental health were compared between subgroups: neuroticism (UKB field 20127(26)), PHQ-9(27), generalised anxiety disorder 7 (GAD-7)(28) and wellbeing(22). The PHQ-9, GAD-7, and wellbeing scores were calculated utilising participants responses to MHQ questions as described by Davis *et al*.(22). A higher neuroticism, PHQ-9 and GAD-7 score represented increased severity. The wellbeing score was coded such that a higher score represented better wellbeing. Not all individuals had measures for all scores, samples sizes for each score can be found in **Supplementary Table 1**.

**Genetic Analyses**

***Genome-wide Association Studies (GWAS)***

For each depression subgroup both case-control and case-only GWAS were performed. Case-only GWAS compared ↑WS to ↓WS, ↑WS to non-↑↓WS and ↓WS to non-↑↓WS. All GWAS were conducted using Plink 1.9(29, 30), with a genome-wide significant threshold of $p < 5 \times 10^{-8}$ and suggestive significance threshold of $p < 1 \times 10^{-5}$. Post-GWAS analyses were performed in FUMA(31). All SNPs of suggestive significance ($p < 1 \times 10^{-5}$) and independent of one another at $r^2 < 0.6$ were identified, independent lead SNPs were then defined as those independent from one another at $r^2 < 0.1$. Genome-wide significance for gene-based tests (performed using MAGMA(32) as part of post-GWAS analyses) was defined as $p < 3 \times 10^{-6}$ after Bonferroni correction for multiple testing, as there were 16,686

protein coded genes included in the analysis. In FUMA, traits previously associated with candidate SNPs (SNP in LD ($r^2$ = 0.6) with independent SNPs of suggestive significance) were identified from the GWAS catalog(33) (https://www.ebi.ac.uk/gwas/). Additionally, GWAS catalog entries of genes encompassing SNPs of genome-wide significance were also examined using GeneCards(34) (www.genecards.org).

***SNP Heritability and Genetic Correlation Analyses***

Two methods for calculating SNP heritability were utilised (i) genome-based restricted maximum likelihood (GREML) implemented using GCTA(35) and (ii) LD score regression (using GWAS summary statistics) implemented using LDSC(36). The observed heritability was converted to the liability scale using a transformation described by Lee et al. (37) implemented in GEnetic Analysis Repository (GEAR) (https://sourceforge.net/p/gbchen/wiki/Hong%20Lee%27s%20Transformation%20for%20Heritability/). This heritability transformation requires a prevalence estimate, however there is a high degree of uncertainty in the prevalence of subgroups defined using reversed neurovegetative symptoms, as prevalence can vary greatly depending on the definition used(13). Therefore, both a point estimate based on sample prevalence and a range of heritability estimates using a range of prevalence values assumed to be reasonable based on the existing literature were calculated. Genetic correlations between subgroups and between subgroups and MDD using a sample that does include UK Biobank(18) were calculated using LD score regression, from GWAS summary statistics, as this method is robust to sample overlap(36, 38). Heritability point estimates and genetic correlations of each subgroup were compared using a z-test:

$$Z = \text{Estimate 1} - \text{Estimate 2} / \sqrt{(\text{Standard Error 1})^2 + (\text{Standard Error 2})^2}$$

**Neurological and Inflammatory Disease Prevalence between Subgroups**

Disease cases of epilepsy, migraine, multiple sclerosis, dementia, Crohn's disease, ulcerative colitis, rheumatoid arthritis, asthma and eczema were identified using ICD10 codes in electronic health records or non-cancer illness self-reported to a trained nurse at in person assessment (UKB field 20002). Codes used to identify cases are shown in **Supplementary Table 2**. As dementia is an age-related disorder, parental dementia (UKB fields 20107 and 20110, disease code = 10) was used for analysis to reduce the effect of sample age on results. A Chi-square test of independence was utilised to compare disease counts between depression subgroups and between subgroups and controls, unless the expected values of greater than 20% of the cells of any given contingency table were less than 5(39). In which case a Fisher's exact test was used to calculate *p*-values.

**Sensitivity Analyses**

All analyses were repeated in more broadly defined depression subgroups using weight change during their worst episode only. In these analyses, atypical depression was represented by a weight gain subgroup (↑W, n = 5,015), typical depression by a weight loss subgroup (↓W, n = 10,924), and there were 10,723 individuals that were not categorised as weight gain or weight loss, hereby referred to as non-↑↓W (**Supplementary Figure 1**). Additionally, to assess the effect of adjusting for BMI, all genetic analyses were also repeated without adjustment for BMI (UKB field 21001).

## Results

### *Sample and Depression Characteristics*

First, the sample and depression characteristics of the ↑WS, ↓WS and non-↑↓WS subgroups were compared (**Figure 1**, **Supplementary Table 3**). BMI at initial assessment was significantly higher in the ↑WS subgroup (29.72 kg/m$^2$) compared to the ↓WS (25.18 kg/m$^2$) and non-↑↓WS (26.61 kg/m$^2$) subgroups, and significantly lower in the ↓WS subgroup compared to non-↑↓WS. It has been previously reported(12) that, when compared to non-↑WS depression, the ↑WS subgroup had a significantly higher proportion of females (77.11%), lower age of onset (32.42 years) and higher median number of episodes (3 episodes). These results remained when the subgroup was compared to the non-↑↓WS subgroup (65.02% female, 35.32 years and 1 episode, **Figure 1a-c**). There was also no significant difference in the proportion of females between the ↑WS and ↓WS subgroups (76.52% female, **Figure 1a**) as observed by Brailean *et* al. (12). Additionally, including the comparison of ↓WS and non-↑↓WS subgroups in analyses, revealed several differences in their depression characteristics. Firstly, the mean age of onset in the ↓WS subgroup (36.68 years) was significantly higher than that of the non-↑↓WS group (35.32 years, **Figure 1b**). Also, even though there was no significant difference in the median number of episodes reported by individuals in the ↓WS and non-↑↓WS subgroups (1, **Figure 1c**), the proportion of individuals reporting “Too many [episodes] to count/One episode ran into the next” was significantly lower in the ↓WS subgroup (13.83%) compared to non-↑↓WS (21.59%, **Figure 1d**).

### *Mental Health Scores*

The median neuroticism, PHQ-9 and GAD-7 scores were significantly higher in the ↑WS subgroup than in both the ↓WS and non-↑↓ WS subgroups (**Figure 1e-g**). All three scores were significantly lower in the ↓WS subgroup compared to the ↑WS and non-↑↓ WS subgroups (**Figure 1e-g, Supplementary Table 3**). Additional analyses investigated the

individual depressive symptoms experienced in more than half of the days in the last two weeks, as examined in the PHQ-9. These showed a significantly higher proportion of ↑WS individuals reported experiencing each symptom examined compared to both the ↓WS and non-↑↓WS subgroups. Also, consistent with the overall PHQ-9 score results, a significantly lower proportion of individuals in the ↓WS group reported PHQ-9 symptoms compared to non-↑↓WS individuals (**Figure 2**). The median wellbeing score was significantly higher in the ↓WS subgroup compared to both the ↑WS and non-↑↓ WS subgroups and significantly lower in the ↑WS group compared to non-↑↓ WS (**Figure 1h**). In previous analyses in the UK Biobank, ↑WS depression has been associated with higher rates of obesity, cardiovascular disease and metabolic syndromes (12). As the wellbeing score contains a measure for happiness with health, it is possible that this measure alone was driving the lower overall wellbeing scores observed in ↑WS depression. However, investigation of the individual measures contained within the wellbeing score ('General happiness', 'Happiness with health', 'Life thought to be meaningful') showed that, compared to the non-↑↓WS individuals, the ↑WS subgroup had a significantly lower score and the ↓WS subgroup a significantly higher score in each individual measure ($p < 0.001$) (**Supplementary Table 4**).

***Genetic Analyses***

In order to better understand the genetic architecture of depression subgroups defined by sleep and weight changes, case-control GWAS, case-only GWAS, SNP heritability and genetic correlation analyses were performed. In the case-control analyses, three loci were associated at genome-wide significance ($p < 5 \times 10^{-8}$) with ↑WS depression: rs7608034 (Anaplastic lymphoma kinase (*ALK*), $p = 3.09 \times 10^{-8}$, **Supplementary Figure 7**), rs1554675 (Ephrin receptor B1 (*EPHB1*), $p = 8.29 \times 10^{-10}$, **Supplementary Figure 8**) and rs1426041 (Calsyntenin 2 (*CLSTN2*), $p = 5.12 \times 10^{-11}$, **Supplementary Figure 9**) (**Figure 3a, Supplementary Table 8**). The *CLSTN2* locus was also associated with a 'suggestive' threshold for significance ($p < 1 \times 10^{-5}$) in case-only GWAS of ↑WS & ↓WS and ↑WS & non-↑↓WS. Whereas the *ALK* and *EPHB1* loci were only nominally significant in case-only

analyses ($p < 9.78\ 10^{-3}$) (**Figure 3b**). There were no genome-wide significant loci observed for the ↓WS and non-↑↓WS depression subgroups, but there were several lead SNPs surpassing the suggestive threshold for significance (**Figure 3a**). Three of the suggestive lead SNPs in case control analyses were located in genes significant in MAGMA gene-based tests ($p < 3 \times 10^{-6}$). *RGS14* was associated with ↑WS depression ($p = 3.76 \times 10^{-7}$), *AKNAD1* was associated with ↓WS ($p = 1.14 \times 10^{-6}$) and *ZNF365* was associated with non-↑↓WS ($p = 1.15 \times 10^{-6}$).

Point estimates of SNP heritability ($h^2_{SNP}$) converted from the observed to the liability scale using sample prevalence ranged from 0.002-0.065 using GREML (**Figure 4a**) and 0.092-0.13 using LD score regression (**Figure 4b**, **Supplementary Table 5**). Although, it is important to note that the $h^2_{SNP}$ estimate for ↑WS depression was not significant in the GREML analyses ($h^2_{SNP} = 0.0021$, SE = 0.036, $p = 0.477$). There were no significant differences in the point estimates of $h^2_{SNP}$ between subgroups in either method used (**Figures 4a & b**, **Supplementary Figures 5 & 6**, **Supplementary Table 5**). As sample prevalence estimates may not be representative of population prevalence, $h^2_{SNP}$ estimates were also converted to the liability scale using a range of prevalences. Across the range of estimates calculated, no significant differences were observed between subgroups.

LD score regression was also used to calculate the genetic correlations (rg) between subgroups and a large non-UK Biobank MDD sample(18). The ↑WS subgroup had the lowest correlation with MDD (rg = 0.40, SE = 0.15, $p = 8.20 \times 10^{-3}$), significantly lower than that of the non-↑↓WS subgroup (rg = 0.91, SE = 0.09, $p = 4.32 \times 10^{-22}$) ($p = 4.85 \times 10^{-3}$), but not significantly lower than that of ↓WS (rg = 0.74, SE = 0.11, $p = 2.75 \times 10^{-12}$) (**Figure 4c**, **Supplementary Table 6**). The genetic correlations (rg) between subgroups were consistent with those previously observed in the UK Biobank(9). The lowest genetic correlations were observed between ↑WS and ↓WS depression (rg = 0.56, SE = 0.22, $p = 0.012$) and ↑WS and non-↑↓WS depression (rg = 0.59, SE = 0.19, $p = 1.80 \times 10^{-3}$). However, these were not

significantly lower than the genetic correlation between ↓WS and non-↑↓WS depression (rg = 0.98, SE = 0.12, $p = 4.89 \times 10^{-17}$) (**Figure 4c**).

***Prevalence of Neurological and Inflammatory Disorders***

In order to investigate potential differences in neurological and inflammatory disease prevalence between the subgroups, cases of nine disorders of interest (epilepsy, migraine, multiple sclerosis, dementia, Crohn's disease, ulcerative colitis, rheumatoid arthritis, asthma and eczema) were compared. For the neurological diseases, there was a significant increase in the odds of comorbid epilepsy in the ↑WS subgroup compared to ↓WS (OR = 2.32, 95% CI = 1.45-3.63), non-↑↓WS (2.24, 1.44-3.37) and controls (2.87, 1.88-4.21), suggesting that the increased odds of epilepsy in lifetime MDD (1.35, 1.14-1.60) is largely driven by the ↑WS subgroup. All subgroups examined had significantly higher odds of migraine compared to controls (**Figure 5a**), but the odds of comorbid migraine were also significantly higher in ↑WS depression compared to the ↓WS (1.41, 1.14-1.73) or non-↑↓WS (1.34, 1.09-1.63) subgroups. Interestingly, there was a significant increase in parental dementia in the non-↑↓WS subgroup compared to controls (1.07, 1.01-1.12); and a significant decrease when comparing non-↑↓WS to the ↑WS and ↓WS subgroups (0.83, 0.70-0.97, and 0.92, 0.85-0.99, respectively).

For the inflammatory diseases, lifetime MDD and all the depression subgroups had significantly higher rates of co-morbid asthma and eczema compared to controls (**Figure 5b**). However, increased rates of asthma were also observed in the ↑WS subgroup compared to the ↓WS (1.37, 1.19-1.58) and non-↑↓WS (1.29, 1.12-1.47) subgroups. Lastly, all depression subgroups, except for the ↑WS subgroup (1.27, 0.76-2.01), were observed to have significantly higher rates of rheumatoid arthritis compared to controls (**Figure 5b**). Although the rates of comorbid rheumatoid arthritis were not significantly lower in ↑WS compared to the other weight and sleep subgroups ($p > 0.56$).

***Sensitivity Analyses***

To assess the effect of subgroup definition and adjustment for BMI, analyses were repeated in (i) subgroups defined using weight change only and (ii), in genetic analyses, without adjustment for BMI. For the most part the results observed for the weight only subgroups were consistent with those observed for subgroups defined using weight and sleep. Although there were some exceptions that have been summarised in the **Supplementary Information**. Of note, the genetic correlation between the weight and sleep change subgroup and their weight only counterpart was also the lowest for the atypical subgroups (rg = 0.86, SE = 0.18, $p = 1.11 \times 10^{-6}$), albeit not statistically significantly lower than the typical (rg = 1.00, SE = 0.015, $p = 0.00$) and non-atypical/typical (rg = 0.97, SE = 0.018, $p = 0.00$) subgroups. Additionally, the loci associated with ↑WS depression were not significantly associated with ↑W depression and their estimated effect was significantly lower ($p < 7.46 \times 10^{-5}$) (**Figure 6**). Performing analyses unadjusted for BMI showed that the GREML $h^2_{SNP}$ of the subgroups representing atypical depression tended to be lower when an adjustment for BMI was applied. However, there was a large degree of uncertainty around estimates (**Supplementary Figure 15**). No genome-wide significant loci were identified in subgroup specific GWAS unadjusted for BMI and the estimated effect sizes of loci that were genome-wide significant in analyses adjusted for BMI were also observed to be significantly lower when no prior adjustment for BMI was made ($p < 0.05$) (**Figure 6**). Finally, a further locus of interest, rs4688064 (located in the *LSAMP* gene) was observed just above genome-wide significance ($p = 5.36 \times 10^{-8}$) in the case-only analyses of ↑W and ↓W unadjusted for BMI The estimated effect of this locus was observed to be reversed in the 'atypical' and 'typical' subgroups (**Figure 6**). Further details can be found in the **Supplementary Information**.

## Discussion

The aim of this study was to extend the investigations of depression subgroups defined using sleep and weight changes, building on previous work in the UK Biobank(9, 12, 17). Analyses examined the differences in depression characteristics, mental health scores, genetic architecture and neurological and inflammatory disease prevalence between three depression subgroups: (i) ↑WS, (ii) ↓WS, and (iii) individuals not falling into either subgroup (non-↑↓ WS). Additionally, the use of broader weight only subgroup definitions and the effect of adjustment for BMI on genetic analyses were explored in an attempt to determine the optimal method for investigating these subgroups in the future.

It is common in analyses of atypical depression, regardless of definition, to primarily compare to a group of non-atypical individuals. However, significant differences were observed between all three depression subgroups examined. The results from the comparisons of depression characteristics and mental health scores suggest that the subgroups fall along a spectrum, regardless of whether they are defined using weight and sleep change or weight change only. At one end of the spectrum lies 'typical' depression, where individuals report decreased weight and sleep or decreased weight during their worst episode, and showed higher ages of onset, higher wellbeing scores, lower neuroticism, PHQ-9 and GAD-7 scores. This subgroup also contained a significantly lower proportion of individuals reporting they lost count of the number of their depressive episodes or that one episode ran into the next. At the other end lies 'atypical' depression, which includes individuals reporting increased weight and sleep or increased weight, a lower age or onset, lower wellbeing scores, higher neuroticism, PHQ-9 and GAD-7 scores, as well as a higher proportion of individuals reporting numerous or continuous episodes. It is possible this represents a spectrum of severity, however as the PHQ-9, GAD-7 and wellbeing score assess mental health at the time of initial assessment not during worst episode, another potential explanation is that the ↑WS and ↓WS symptoms discriminate between chronic and acute depression subgroups.

Genome-wide association studies of the depression subgroups identified three loci associated with ↑WS depression: rs7608034 (*ALK*), rs1554675 (*EPHB1*) and rs1426041 (*CLSTN2*) and, in additional gene-based tests, three genes were observed to be associated with the subgroups: *RGS14*, *AKNAD1* and *ZNF365*. Of these genes only three have previous associations with MDD or depression related phenotypes: *ALK*(40), *CLSTN2*(41) and *AKNAD1*(42). Of note, the *AKNAD1* gene contains a locus previously reported as negatively associated with recurrent MDD(42). This is consistent with the ↓WS and ↓W subgroups as both were observed to have a significantly lower proportion of individuals reporting 'Too many [episodes] to count' or 'One [episode] ran into the next'. Interestingly, all three loci associated with ↑WS depression were also found to been previously associated with response or adverse reaction to anticonvulsants(43-45)(see below). The results of subgroup-specific association analyses also provide further evidence of a relationship between atypical depression and obesity. The genes *ALK*(46), *CLSTN2*(47), *EPHB1*(47-49), have all previously been associated with BMI, despite being detected in analyses corrected for BMI. *ALK* has been previously associated with adiponectin levels adjusted for BMI(50) and is postulated to be a candidate 'thinness gene', as knockdown in *Drosophila* has been shown to lead to reduced triglyceride levels and deletion in mice resulted in resistance to diet- and leptin-mutation-induced obesity(51). *CLSTN2* is associated with visceral adipose tissue adjusted for BMI(52) and *RGS14* is thought to play a role in beta-adrenergic receptor signalling, which regulates lipid metabolism(53) and knockout has been reported to lower body weight and improve body composition in mice(54). In contrast, the gene associated with ↓WS and ↓W depression, *AKNAD1*, has previously been positively associated with lower subcutaneous adipose tissue in HIV-infected men(55) and negatively associated with apolipoprotein B measurement(56).

Consistent with previous studies both within and outside the UK Biobank(7-9, 17), there was no statistically significant difference in the SNP heritability between the subgroups and the genetic correlations between subgroups tended to be lowest when comparisons included the

↑WS subgroup(9). However, these analyses are not without limitations, the most important of which is the comparatively small sample size of the ↑WS subgroup (n= 1,525). The fact that the SNP heritability estimates for the ↑WS subgroup were at most only nominally significant could be the result of a lack of power. The limited sample and its potential effect on the SNP heritability and genetic correlation estimates make it difficult to draw firm conclusions on the effect of broader weight-only subgroup definitions and of correcting analyses for BMI. Although the ↑W subgroup was larger (n = 5,015) and observed to have many similar characteristics to the ↑WS subgroup, these subgroups were observed to have the lowest genetic correlation when subgroups defined by weight and sleep change were compared to their weight only counterpart. In addition, the trend that genetic correlations with the ↑WS subgroup were lower than with the other subgroups was not observed when utilising weight only to define subgroups. Therefore, it seems reasonable going forward to focus analyses on depression subgroups defined using weight and sleep changes, to avoid reducing the specificity of the sample by introducing as few potentially non-atypical individuals as possible.

SNP heritability and genetic correlation estimates of the ↑WS and ↑W subgroups tended to be lower after adjustment for BMI, but not significantly so. This may also be the as a result of insufficient power, as there was a high level of uncertainty around estimates. Given the further evidence for an association between the ↑WS subgroup and obesity reported above, it is crucial to unravel both the relationship between atypical depression and obesity and the full implications of correcting for BMI in analyses.

In addition to the previously reported cardiovascular and metabolic diseases associated with atypical depression in the UK Biobank(12), these analyses suggest there is a higher number of individuals with epilepsy, migraine and asthma in the ↑WS subgroup compared to the other depression subgroups. In fact, the increased prevalence of epilepsy in lifetime MDD compared to controls appears to be driven almost entirely by the ↑WS subgroup. Epilepsy was included in investigations of the prevalence of disorders between depression subgroups

as a result of the GWAS of ↑WS. All three ↑WS genome-wide significant loci implicated genes which had been previously associated with response or reaction to anticonvulsant medications(43-45). These anticonvulsants (carbamazepine, lamotrigine and valproate) are also well recognised mood stabilisers, and are established treatment options in bipolar disorder(57), which is observed at higher rates in atypical compared to non-atypical depression across DSM-V and neurovegetative definitions(12, 13). Interestingly, an anticonvulsant was recently identified as having a significant negative connectivity score with treatment resistant depression(58), which is suggestive of drug reversal of a disease signature(59). The same study also reported an association between reduced risk of treatment resistant depression and MDD with ↓WS symptoms, as well as an increased risk in individuals with ↑W. A similar trend was observed for MDD with ↑WS symptoms, but the association was not significant after correction for multiple testing(58).

Lastly, there are several limitations, in addition to the relatively small sample of ↑WS individuals, to consider alongside these results. First, the UK Biobank cohort is not considered to be highly representative of the general population. There is evidence of 'healthy volunteer' selection bias in UK Biobank and participants are more likely to be female, older and live in less socioeconomically deprived areas(60). In addition, analyses were restricted to those in the White British ancestry cluster, reducing the potentially confounding effects of population stratification, but at the cost of further limiting the generalisability of findings. In addition, both lifetime MDD and the depression subgroups were defined using self-reported depression symptoms which could be subject to recall bias. Finally, It is also important to note that despite being the reported as highly discriminatory, weight and sleep symptoms are only a subset of those described in the DSM-V criteria for atypical depression(3), and it was not possible to include information on appetite change, reported as the most discriminatory symptom by Milaneschi *et al.*(7), due to data constraints.

In conclusion, there are significant differences in depression characteristics and mental health scores between the three depression subgroups examined here, which potentially

identify more chronic and acute forms of MDD. Future analyses should continue to investigate all three subgroups, as using only an atypical and non-atypical subgroup may result in important differences being overlooked. In addition, several novel genetic associations with ↑WS depression were identified, which provide further evidence for a relationship between obesity and atypical depression and highlight a previously unreported potential association between atypical depression and epilepsy, which appears to drive the overall association between epilepsy and lifetime MDD. Further work is needed to fully understand the relationship between atypical depression and both obesity and adjusting analyses for BMI, as well as epilepsy and anticonvulsants. Finally, an important limitation of these analyses was the small sample of ↑WS depression individuals, therefore it would be highly beneficial to repeat these analyses in larger, independent samples.

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This research has been conducted using data from UK Biobank, a major biomedical database (https://www.ukbiobank.ac.uk/).

## Conflict of Interest

The authors declare no conflicts of interest.

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## Figure Legends

**Figure 1**. The sample and depression characteristics: (a) the proportion of females (%), (b) age of onset, (c) number of depressive episodes, (d) proportion reporting 'Too many episodes to count' or 'One episode ran into the next' and the mental health scores: (e) neuroticism, (f) patient health questionnaire 9 (PHQ-9), (g) generalised anxiety disorder 7 (GAD-7) and wellbeing in the ↑WS, ↓WS and non-↑↓WS depression subgroups. Proportions are shown as exact values in bar charts. Otherwise, the distribution of data is shown as a violin plot, boxplots within each violin plot show the median and interquartile range (IQR), whiskers for each boxplot are calculated using the formula: quartile + 1.5*IQR, outliers were considered to be any value outside this formula and are not shown. For (c) number of episodes, there were 109 individuals reporting >20 episodes that are not shown in the figure. The yellow diamond denotes the mean of each subgroup. Significant comparisons are denoted as follows: *** ($p < 0.001$), ** ($p < 0.01$), * ($p < 0.05$), NS ($p > 0.05$).

**Figure 2**. A heat map of the proportion of individuals who report experiencing each of the PHQ-9 symptoms 'more than half the days' or 'nearly every day' over the last two weeks, at the time of completing the UK Biobank mental health questionnaire, for the ↑WS, ↓WS and non-↑↓WS depression subgroups.

**Figure 3.** Manhattan plots of (a) the case-control GWAS results (top = ↑WS depression, middle = ↓WS depression, bottom = non-↑↓WS) and (b) the case-only GWAS results (top = ↑WS depression and ↓WS depression, middle = ↑WS depression and non-↑↓WS depression, bottom = ↓WS depression and non-↑↓WS depression). Chromosomal location is on the x-axis and $-\log_{10}$ of the *p*-value for each SNP is on the y-axis. The red line indicates the threshold for genome-wide significance ($p < 5 \times 10^{-8}$) and the blue dashed line indicates the threshold for "suggestive" significance ($p < 1 \times 10^{-5}$).

**Figure 4**. The results of the SNP heritability (a & b) and genetic correlation (c) analyses. SNP heritability estimates calculated using (a) genome-based restricted maximum likelihood (GREML) and (b) LD score regression are shown. SNP heritability was converted to the liability scale across a range of prevalences plotted as a solid line, with dashed lines representing the 95% confidence intervals of the estimates. The SNP heritability estimate at sample prevalence is denoted by a point and error bar. In SNP heritability plots (a & b) the black dashed line shows the estimated SNP heritability of depression(20). Genetic correlations, their 95% confidence intervals and corresponding *p*-values are shown in plot (c). The black dashed line corresponds to a genetic correlation of 1.

**Figure 5**. The odds ratios and 95% confidence intervals of each depression subgroup compared to controls in (a.) four neurological and (b.) five inflammatory disorders of interest.

**Figure 6**. A heat map of the estimated effects of the four SNPs (rs7608034, rs1554675, rs1426041 and rs4688064) nearing or below genome-wide significance in at least one GWAS in each GWAS performed. Significance is denoted as follows: * = nominal significance ($p < 0.05$), ** = suggestive significance ($p = 1 \times 10^{-5}$) and *** = genome-wide significance ($p < 5 \times 10^{-8}$).

**Figure 1.**

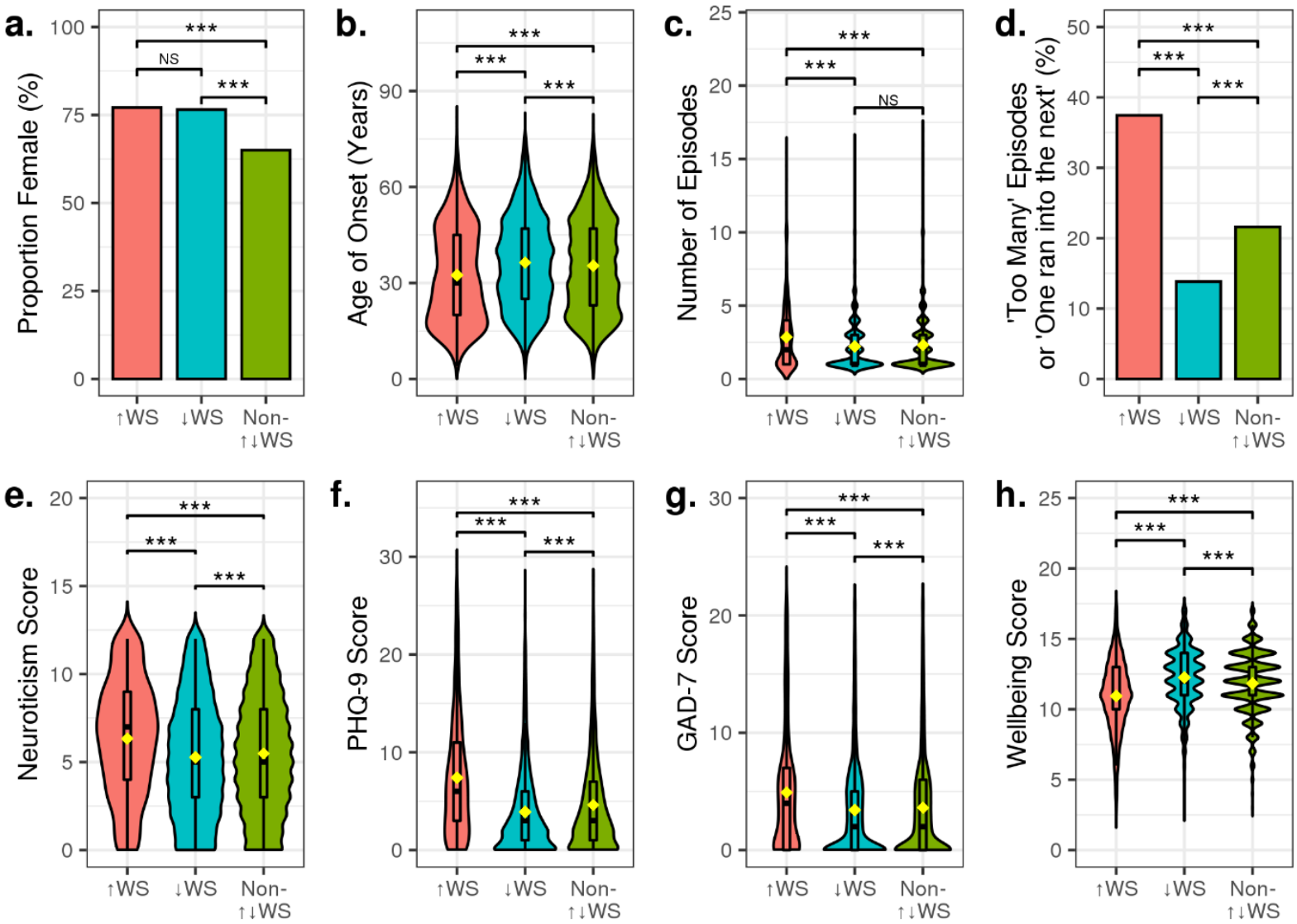

a.
Proportion Female (%)
100
75
50
25
0
***
NS
***
↑WS
↓WS
Non-↑↓WS
b.
Age of Onset (Years)
90
60
30
0
***
***
***
c.
Number of Episodes
25
20
15
10
5
0
***
***
NS
d.
'Too Many' Episodes or 'One ran into the next' (%)
50
40
30
20
10
0
***
***
***
e.
Neuroticism Score
20
15
10
5
0
***
***
***
f.
PHQ-9 Score
30
20
10
0
***
***
***
g.
GAD-7 Score
30
20
10
0
***
***
***
h.
Wellbeing Score
25
20
15
10
5
0
***
***
***

**Figure 2.**

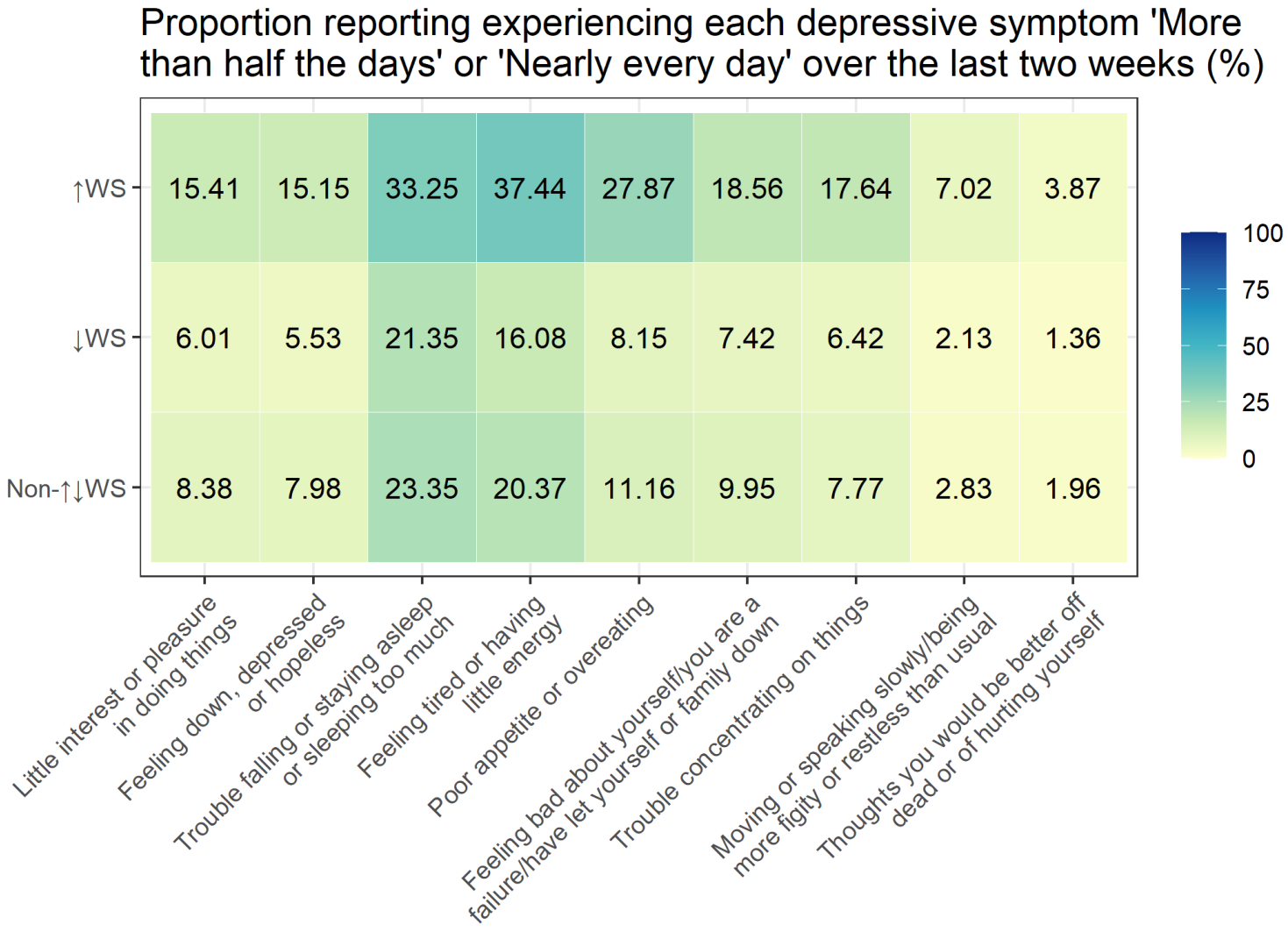

Proportion reporting experiencing each depressive symptom 'More than half the days' or 'Nearly every day' over the last two weeks (%)
↑WS
↓WS
Non-↑↓WS
15.41
15.15
33.25
37.44
27.87
18.56
17.64
7.02
3.87
6.01
5.53
21.35
16.08
8.15
7.42
6.42
2.13
1.36
8.38
7.98
23.35
20.37
11.16
9.95
7.77
2.83
1.96
Little interest or pleasure in doing things
Feeling down, depressed or hopeless
Trouble falling or staying asleep or sleeping too much
Feeling tired or having little energy
Poor appetite or overeating
Feeling bad about yourself/you are a failure/have let yourself or family down
Trouble concentrating on things
Moving or speaking slowly/being more figity or restless than usual
Thoughts you would be better off dead or of hurting yourself
100
75
50
25
0

**Figure 3.**

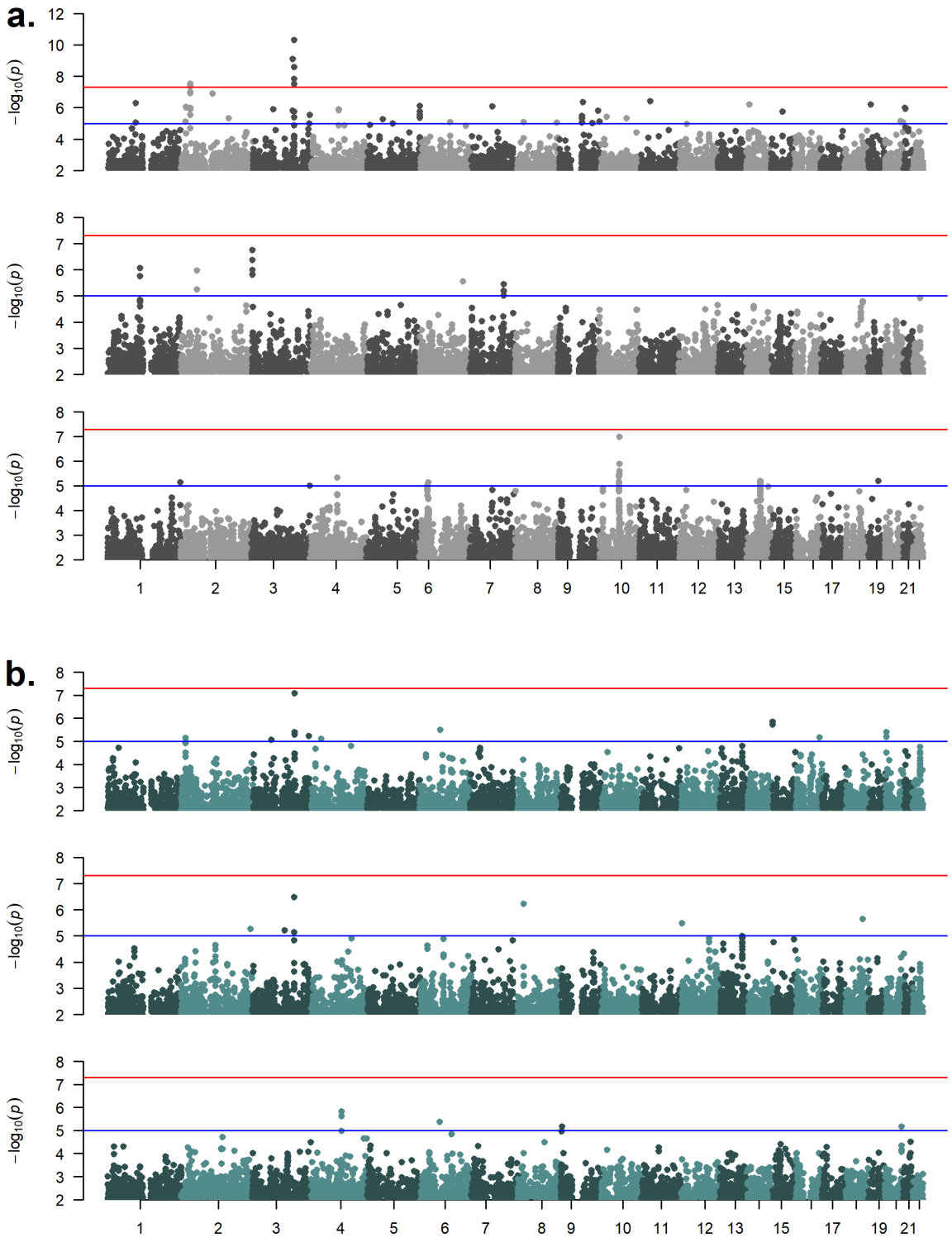


**Figure 4.**

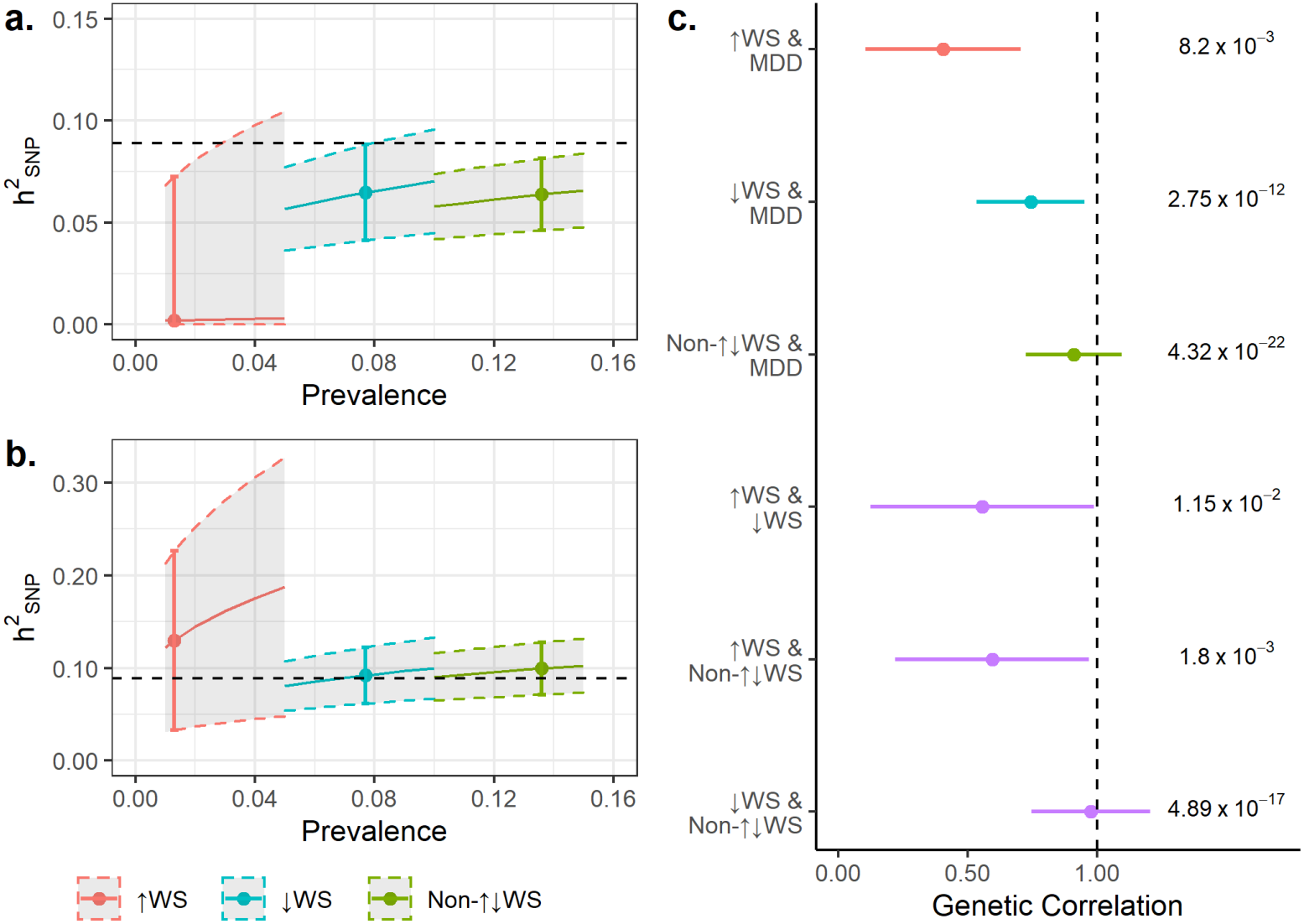

a.
0.15
0.10
0.05
0.00
$h^2_{SNP}$
0.00
0.04
0.08
0.12
0.16
Prevalence
b.
0.30
0.20
0.10
0.00
$h^2_{SNP}$
0.00
0.04
0.08
0.12
0.16
Prevalence
↑WS
↓WS
Non-↑↓WS
c.
↑WS & MDD
↓WS & MDD
Non-↑↓WS & MDD
↑WS & ↓WS
↑WS & Non-↑↓WS
↓WS & Non-↑↓WS
$8.2 \times 10^{-3}$
$2.75 \times 10^{-12}$
$4.32 \times 10^{-22}$
$1.15 \times 10^{-2}$
$1.8 \times 10^{-3}$
$4.89 \times 10^{-17}$
0.00
0.50
1.00
Genetic Correlation

**Figure 5.**

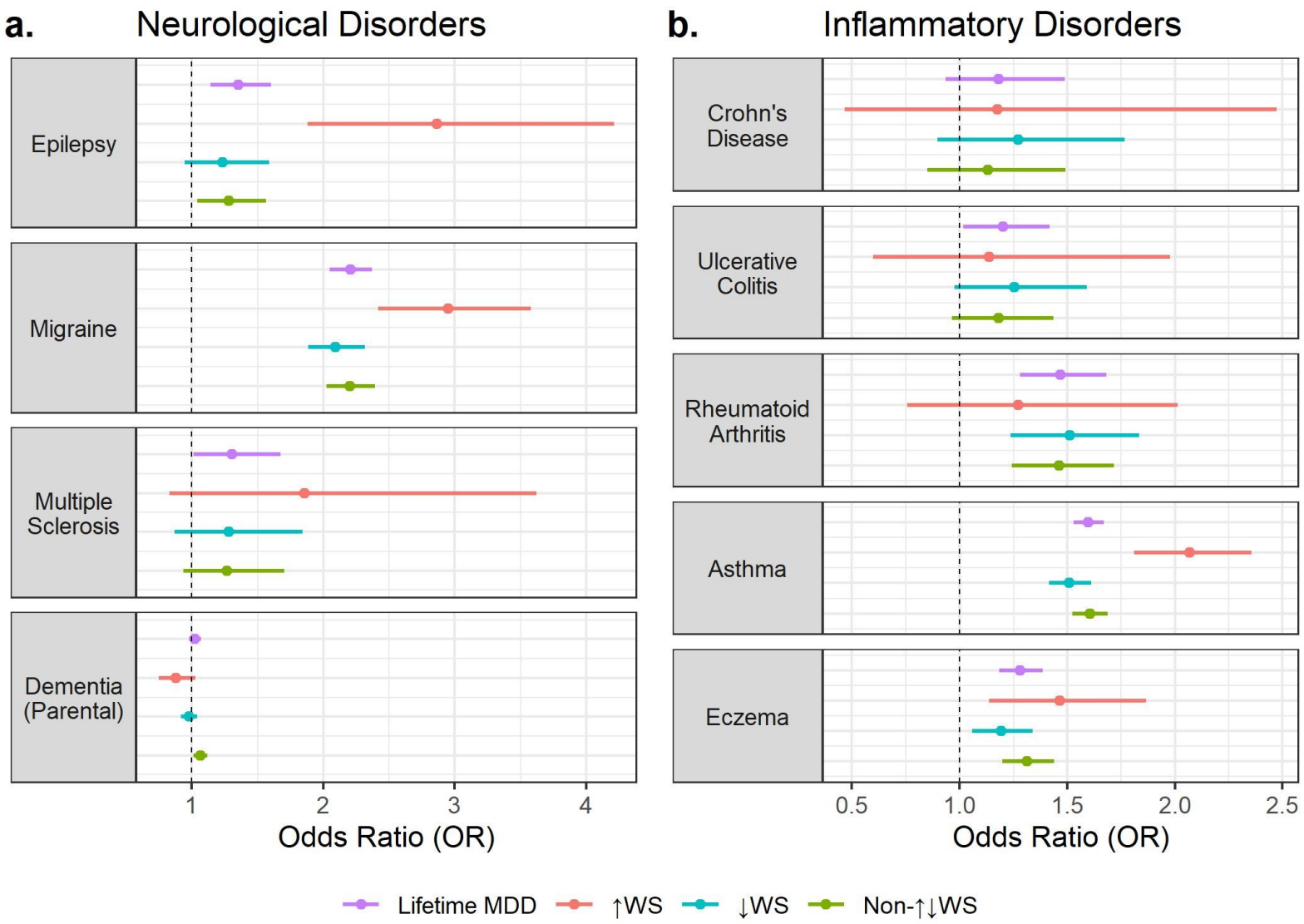
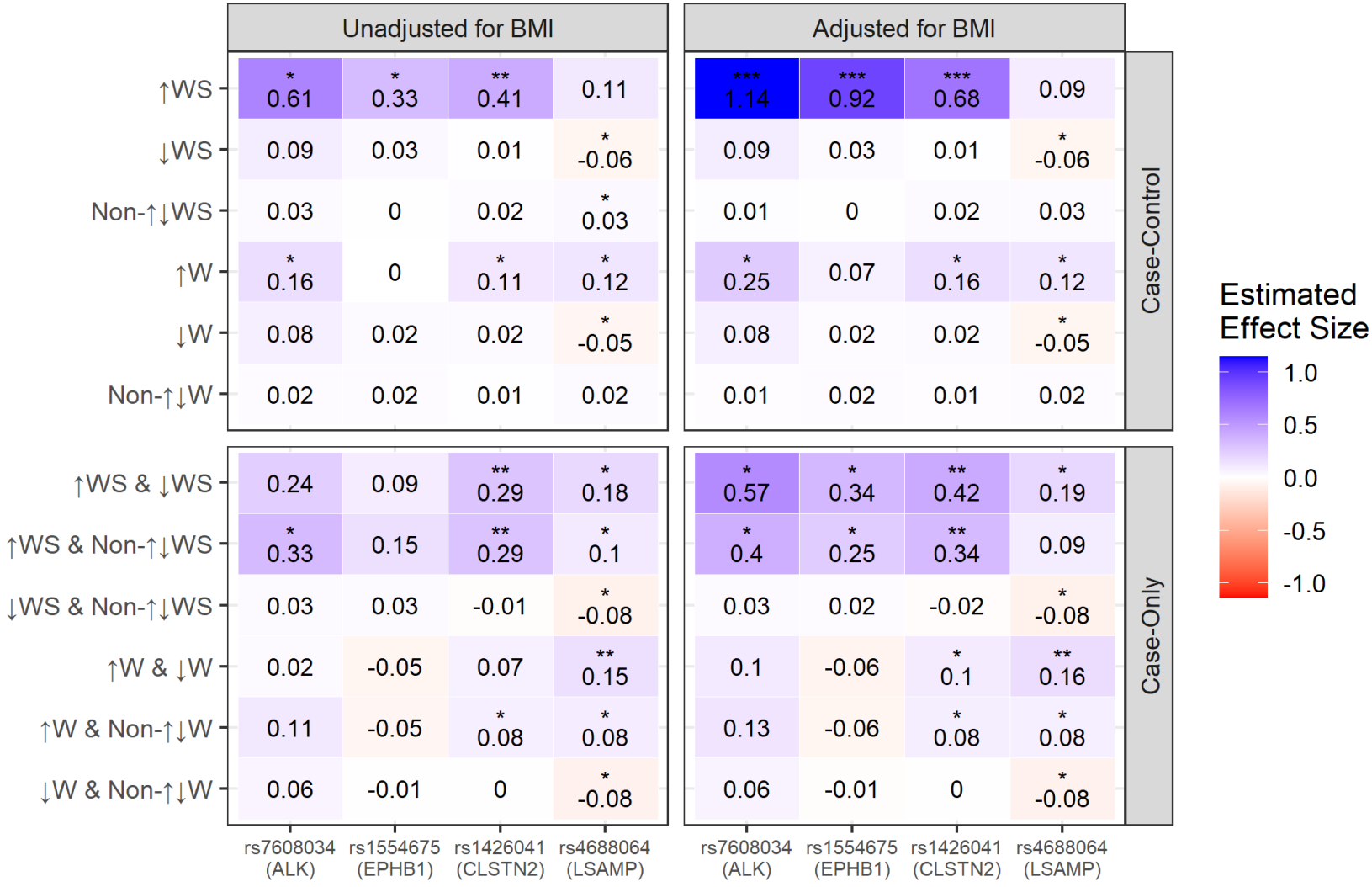

a.
Neurological Disorders
Epilepsy
Migraine
Multiple Sclerosis
Dementia (Parental)
1
2
3
4
Odds Ratio (OR)
b.
Inflammatory Disorders
Crohn's Disease
Ulcerative Colitis
Rheumatoid Arthritis
Asthma
Eczema
0.5
1.0
1.5
2.0
2.5
Odds Ratio (OR)
Lifetime MDD
↑WS
↓WS
Non-↑↓WS

**Figure 6.**


Unadjusted for BMI
Adjusted for BMI
Case-Control
Case-Only
↑WS
↓WS
Non-↑↓WS
↑W
↓W
Non-↑↓W
↑WS & ↓WS
↑WS & Non-↑↓WS
↓WS & Non-↑↓WS
↑W & ↓W
↑W & Non-↑↓W
↓W & Non-↑↓W
rs7608034 (ALK)
rs1554675 (EPHB1)
rs1426041 (CLSTN2)
rs4688064 (LSAMP)
Estimated Effect Size
1.0
0.5
0.0
-0.5
-1.0