Supplementary Materials

Depression with atypical neurovegetative symptoms shares genetic predisposition with immuno-metabolic traits and alcohol consumption

Supplementary Table 1: Summary of genome-wide association studies (GWAS) used to create polygenic risk scores.

Trait	Type of phenotype	N cases	N controls	Ethnicity	Reference
Psychiatric disorders					
Major depressive disorder**	Binary	45,591	97,674	European	(Wray et al., 2018)
Bipolar disorder	Binary	20,352	31,358	European	(Stahl et al., 2019)
Schizophrenia	Binary	36,989	113,075	European	(Ripke et al., 2014)
Anxiety disorders	Binary	7,016	14,745	European	(Otowa et al., 2016)
Alcohol dependence	Binary	14,904	37,944	Trans-ethnic	(Walters et al., 2018)
PTSD	Binary	5,131	15,092	Trans-ethnic	(Duncan et al., 2018)
Anorexia nervosa*	Binary	16,992	55,525	European	(Watson et al., 2019)
Alcohol use and smoking					
Alcohol daily use	Continuous	70,460		European	(Schumann et al., 2016)
N cigarettes per day	Continuous	38,181		European	(Tobacco and Genetics Consortium, 2010)
Cannabis use lifetime	Binary	14,374	17,956	European	(Stringer et al., 2016)
Personality traits					
Extraversion	Continuous	63,030		European	(van den Berg et al., 2016)
Neuroticism	Continuous	63,030		European	(Genetics of Personality Consortium et al., 2015)
Cardio-metabolic traits					
Type 2 diabetes	Binary	26,676	132,532	Trans-ethnic	(Scott et al., 2017)
Coronary artery disease	Binary	60,801	123,504	European and south Asian	(Nikpay et al., 2015)
Triglycerides	Continuous	188,577		Trans-ethnic	(Willer et al., 2013)
Total LDL cholesterol	Continuous	188,577		Trans-ethnic	(Willer et al., 2013)
Total HDL cholesterol	Continuous	188,577		Trans-ethnic	(Willer et al., 2013)
BMI	Continuous	322,154		European	(Locke et al., 2015)
Leptin	Continuous	31,816		European	(Kilpeläinen et al., 2016)
Leptin adjusted for BMI	Continuous	31,816		European	(Kilpeläinen et al., 2016)
CRP	Continuous	204,402		European	(Ligthart et al., 2018)
Ischemic stroke	Binary	67,162	454,450	Trans-ethnic	(Malik et al., 2018)

** Subjects included in UK Biobank and 23AndMe were excluded from the analyses

* This sample had a marginal overlap (2% of cases) with UK biobank depressed sample included in these analyses

Supplementary Table 2: A. PRS results for ↑WS depression (n=1,854) vs. depression without ↑WS (n=28,215) (including bipolar disorder and/or schizophrenia cases, the results were similar when excluding these groups, see Supplementary Figure 2). **B.** Nagelkerke R2 was reported on the observed scale (prevalence of ↑WS depression among people with major depression in UK Biobank = 0.066) and considering other plausible prevalence values of ↑WS depression among people with major depression (these comparisons included only cases and not healthy controls). **C.** Results obtained by comparing individual neurovegetative symptoms for the significant PRS and leptin adjusted for BMI for comparison with the main results. Significant results are in bold.

A.

Trait	Best p threshold	Beta (SE)	P	OR (95% CI)
Major depressive disorder	0.3	0.09 (0.02)	1.14e-04**	1.10 (1.05-1.15)
Bipolar disorder	1e.5	0.05 (0.02)	0.05	1.05 (1-1.10)
Schizophrenia	0.01	0.03 (0.02)	0.15	1.04 (0.99-1.09)
Anxiety disorders	0.3	0.04 (0.02)	0.13	1.04 (0.99-1.09)
Alcohol dependence	1e-05	-0.05 (0.02)	0.04*	0.95 (0.91-0.99)
PTSD	0.01	0.05 (0.02)	0.03*	1.05 (1-1.10)
Anorexia nervosa	0.4	-0.04 (0.02)	0.08	0.96 (0.91-1)
Alcohol daily use	0.4	-0.13 (0.03)	1.04e-05**	0.88 (0.83-0.93)
N cigarettes per day	5e-08	0.04 (0.02)	0.08	1.04 (0.99-1.09)
Cannabis use lifetime	1e-05	0.03 (0.02)	0.14	1.04 (0.99-1.09)
Extraversion	0.001	0.03 (0.02)	0.28	1.03 (0.98-1-08)
Neuroticism	0.001	-0.03 (0.02)	0.27	0.97 (0.93-1.02)
Type 2 diabetes	0.001	0.07 (0.02)	0.005*	1.07 (1.02- 1.12)
Coronary artery disease	0.5	0.07 (0.02)	0.007*	1.07 (1.02- 1.12)
Triglycerides	1	0.06 (0.02)	0.02*	1.06 (1.01-1.11)
Total LDL cholesterol	1e-05	-0.04 (0.02)	0.08	0.96 (0.92-1)
Total HDL cholesterol	0.3	-0.06 (0.02)	0.02*	0.94 (0.90-0.99)
BMI	0.001	0.18 (0.02)	2.37e-14**	1.20 (1.15-1.26)
Leptin	0.001	0.09 (0.02)	2.99e-04*	1.09 (1.04-1.14)
Leptin adjusted for BMI	0.3	0.03 (0.02)	0.28	1.03 (0.98-1.08)
CRP	0.4	0.11 (0.02)	8.86e-06**	1.11 (1.06-1.17)
Ischemic stroke	0.4	0.06 (0.02)	0.01*	1.06 (1.01-1.12)

* $p < 0.05$; ** $p < 2.1e-04$

B.

Trait	Observed scale (K=0.066)	K=0.10	K=0.15	K=0.20
Major depressive disorder	0.00133	0.00224	0.00255	0.00278
Bipolar disorder	0.00035	0.00059	0.00067	0.00074
Schizophrenia	0.00018	0.00031	0.00035	0.00038
Anxiety disorders	0.00020	0.00034	0.00038	0.00042
Alcohol dependence	0.00037	0.00062	0.00070	0.00078
PTSD	0.00041	0.00069	0.00079	0.00086
Anorexia nervosa	0.00028	0.00047	0.00053	0.00058
Alcohol daily use	0.00174	0.00292	0.00332	0.00363

N cigarettes per day	0.00027	0.00046	0.00052	0.00057
Cannabis use lifetime	0.00020	0.00033	0.00038	0.00041
Extraversion	0.00010	0.00018	0.00020	0.00022
Neuroticism	0.00011	0.00018	0.00020	0.00022
Type 2 diabetes	0.00071	0.00119	0.00135	0.00148
Coronary artery disease	0.00064	0.00108	0.00123	0.00134
Triglycerides	0.00051	0.00086	0.00097	0.00106
Total LDL cholesterol	0.00027	0.00046	0.00052	0.00057
Total HDL cholesterol	0.00052	0.00088	0.0010	0.00109
BMI	0.00520	0.00875	0.00994	0.01085
Leptin	0.00117	0.00197	0.00224	0.00244
Leptin adjusted for BMI	0.00010	0.00017	0.00020	0.00022
CRP	0.00177	0.00297	0.00338	0.00369
Ischemic stroke	0.00055	0.00093	0.00106	0.00116

C.

Depression with weight increase (n=5,801) vs. depression without weight increase (n=20,561):

Trait	Best p threshold	Beta (SE)	P	OR (95% CI)
Major depressive disorder	0.3	0.04 (0.02)	4.97e-03*	1.04 (1.01-1.07)
Alcohol daily use	1	-0.07 (0.02)	1.99e-04**	0.93 (0.90-0.97)
BMI	0.4	0.24 (0.02)	2.53e-56**	1.28 (1.24-1.32)
Leptin	0.1	0.08 (0.01)	6.43e-08**	1.08 (1.05-1.12)
Leptin adjusted for BMI	0.4	0.01 (0.01)	0.61	1.01 (0.98-1.04)
CRP	0.4	0.11 (0.02)	3.09e-13**	1.12 (1.08-1.15)

Depression with hypersomnia (n=6,923) vs. depression without hypersomnia (n=18,871):

Trait	Best p threshold	Beta (SE)	P	OR (95% CI)
Major depressive disorder	0.3	0.05 (0.01)	3.98e-04*	1.05 (1.02-1.08)
Alcohol daily use	0.05	-0.03 (0.02)	0.10	0.97 (0.95-1.01)
BMI	1	0.03 (0.01)	0.046*	1.03 (1.00-1.06)
Leptin	0.2	0.03 (0.01)	0.070	1.03 (1.00-1.05)
Leptin adjusted for BMI	1e-05	-0.01 (0.01)	0.48	0.99 (0.96-1.02)
CRP	0.1	0.05 (0.01)	9.94e-04*	1.05 (1.02-1.08)

Supplementary Table 3: A. PRS results for ↑WS depression (n=1,854) vs. ↓WS depression (n=10,142) (including bipolar disorder and/or schizophrenia cases, the results were similar when excluding these groups, see Supplementary Figure 3). **B.** Nagelkerke R2 is reported on the observed scale (prevalence K=0.15 in UK Biobank) and according to different plausible values of prevalence of ↑WS depression among people having depression with neurovegetative symptoms (these comparisons included only cases and not healthy controls). Significant results are in bold.

A

Trait	Best p threshold	Beta (SE)	P	OR (95% CI)
Major depressive disorder	0.3	0.08 (0.03)	1.10e-03*	1.09 (1.03-1.14)
Bipolar disorder	0.4	0.04 (0.03)	0.12	1.04 (0.99-1.10)
Schizophrenia	5e.8	0.02 (0.03)	0.38	1.02 (0.97-1.08)
Anxiety disorders	0.3	0.02 (0.03)	0.39	1.02 (0.97-1.07)
Alcohol dependence	1e-05	-0.06 (0.03)	0.03*	0.95 (0.89-0.99)
PTSD	0.01	0.05 (0.03)	0.05	1.05 (1.00-1.11)
Anorexia nervosa	0.4	-0.06 (0.03)	0.02*	0.94 (0.89-0.99)
Alcohol daily use	0.4	-0.14 (0.03)	1.34e-05**	0.87 (0.82-0.93)
N cigarettes per day	5e-8	0.04 (0.03)	0.11	1.04 (0.99-1.10)
Cannabis use lifetime	1e-5	0.03 (0.03)	0.20	1.03 (0.98-1.08)
Extraversion	0.001	0.03 (0.03)	0.18	1.03 (0.98-1.09)
Neuroticism	0.001	0.03 (0.03)	0.18	0.97 (0.92-1.02)
Type 2 diabetes	0.001	0.08 (0.03)	0.0022*	1.08 (1.03-1.14)
Coronary artery disease	0.5	0.07 (0.03)	0.012*	1.07 (1.01-1.12)
Triglycerides	1	0.06 (0.03)	0.019*	1.06 (1.01-1.12)
Total LDL cholesterol	1e-05	-0.06 (0.03)	0.022*	0.94 (0.90-0.99)
Total HDL cholesterol	0.3	-0.06 (0.03)	0.023*	0.94 (0.90-0.99)
BMI	0.001	0.24 (0.03)	1.80e-20**	1.27 (1.21-1.33)
Leptin	0.3	0.09 (0.03)	6.01e-04*	1.09 (1.04-1.15)
Leptin adjusted for BMI	0.4	0.02 (0.03)	0.35	1.02 (0.97-1.08)
CRP	0.1	0.12 (0.03)	7.33e-06**	1.12 (1.07-1.18)
Ischemic stroke	0.4	0.06 (0.03)	0.016*	1.07 (1.01-1.12)

* $p < 0.05$; ** $p < 2.1e-04$

B

Trait	Observed scale (K=0.15)	K=0.20	K=0.30	K=0.40
Major depressive disorder	0.00152	0.00219	0.00245	0.00259
Bipolar disorder	0.00034	0.00049	0.00055	0.00058
Schizophrenia	0.00011	0.00016	0.00018	0.00019
Anxiety disorders	0.00010	0.00015	0.00017	0.00018
Alcohol dependence	0.00067	0.00097	0.00109	0.00115
PTSD	0.00055	0.00080	0.00089	0.00094
Anorexia nervosa	0.00077	0.00111	0.00124	0.00131

Alcohol daily use	0.00271	0.00391	0.00436	0.00461
N cigarettes per day	0.00037	0.00053	0.00060	0.00063
Cannabis use lifetime	0.00023	0.00033	0.00037	0.00039
Extraversion	0.00025	0.00037	0.00041	0.00043
Neuroticism	0.00026	0.00037	0.00042	0.00044
Type 2 diabetes	0.00134	0.00193	0.00215	0.00228
Coronary artery disease	0.00089	0.00128	0.00143	0.00152
Triglycerides	0.00078	0.00113	0.00126	0.00133
Total LDL cholesterol	0.00075	0.00108	0.00121	0.00127
Total HDL cholesterol	0.00074	0.00106	0.00119	0.00125
BMI	0.01237	0.01783	0.01987	0.02098
Leptin	0.00168	0.00243	0.00271	0.00286
Leptin adjusted for BMI	0.00013	0.00018	0.00020	0.00021
CRP	0.00287	0.00414	0.00463	0.00489
Ischemic stroke	0.00083	0.00119	0.00133	0.00141

Supplementary Table 4: A. PRS results for ↑WS depression (n=1,854) vs. healthy controls (n=8,000) (including bipolar disorder and/or schizophrenia cases, the results were similar when excluding these groups, see Supplementary Figure 4). **B.** Nagelkerke R2 is reported on the liability scale according to different possible values of ↑WS depression prevalence in the population. Significant results are in bold.

A

Trait	Best p threshold	Beta (SE)	P	OR (95% CI)
Major depressive disorder	0.3	0.27 (0.02)	2.39e-28**	1.30 (1.24-1.36)
Bipolar disorder	0.4	0.14 (0.02)	3.04e-08**	1.15 (1.09-1.20)
Schizophrenia	0.4	0.15 (0.02)	4.93e-09**	1.15 (1.10-1.21)
Anxiety disorders	0.3	0.08 (0.02)	3.70e-04*	1.09 (1.04-1.14)
Alcohol dependence	0.5	0.06 (0.02)	0.02*	1.06 (1.01-1.11)
PTSD	0.01	0.07 (0.02)	5.63e-03*	1.07 (1.02-1.12)
Anorexia nervosa	0.2	0.06 (0.02)	0.01*	1.06 (1.01-1.11)
Alcohol daily use	0.2	-0.12 (0.03)	9.31e-06**	0.88 (0.84-0.93)
N cigarettes per day	0.05	0.05 (0.02)	0.05	1.05 (1.00-1.10)
Cannabis use lifetime	0.3	0.04 (0.03)	0.11	1.04 (0.99-1.09)
Extraversion	0.2	-0.03 (0.02)	0.24	0.97 (0.93-1.02)
Neuroticism	0.4	0.07 (0.02)	4.87e-03*	1.07 (1.02-1.12)
Type 2 diabetes	0.001	0.07 (0.02)	4.70e-03*	1.07 (1.02-1.12)
Coronary artery disease	0.5	0.10 (0.02)	1.60e-05**	1.11 (1.06-1.16)
Triglycerides	1	0.09 (0.02)	8.27e-05**	1.10 (1.05-1.15)
Total LDL cholesterol	5e-08	-0.04 (0.02)	0.12	0.96 (0.92-1.01)
Total HDL cholesterol	0.3	-0.07 (0.02)	3.84e-03*	0.93 (0.89-0.98)
BMI	0.3	0.21 (0.02)	1.65e-18**	1.24 (1.18-1.30)
Leptin	0.05	0.10 (0.02)	3.01e-05**	1.10 (1.05-1.16)
Leptin adjusted for BMI	0.5	0.03 (0.02)	0.23	1.03 (0.98-1.08)
CRP	0.5	0.13 (0.02)	1.21e-07**	1.13 (1.08-1.19)
Ischemic stroke	0.4	0.08 (0.02)	1.68e-03*	1.08 (1.03-1.13)

* $p < 0.05$; ** $p < 2.1e-04$

B

Trait	K=0.01	K=0.02	K=0.03	K=0.04	K=0.05
Major depressive disorder	0.00936	0.0111	0.01240	0.01345	0.01436
Bipolar disorder	0.00235	0.00279	0.00311	0.00338	0.00361
Schizophrenia	0.00262	0.00312	0.00348	0.00377	0.00403
Anxiety disorders	0.00097	0.00115	0.00129	0.00140	0.00149
Alcohol dependence	0.00040	0.00047	0.00053	0.00057	0.00061
PTSD	0.00059	0.00070	0.00078	0.00084	0.00090
Anorexia nervosa	0.00048	0.00057	0.00063	0.00069	0.00073

Alcohol daily use	0.00150	0.00179	0.00199	0.00216	0.00231
N cigarettes per day	0.00028	0.00033	0.00037	0.00041	0.00043
Cannabis use lifetime	0.00021	0.00024	0.00027	0.00030	0.00032
Extraversion	0.00011	0.00013	0.00014	0.00015	0.00016
Neuroticism	0.00061	0.00072	0.00080	0.00087	0.00093
Type 2 diabetes	0.00061	0.00073	0.00081	0.00088	0.00094
Coronary artery disease	0.00143	0.00169	0.00189	0.00205	0.00219
Triglycerides	0.00119	0.00141	0.00157	0.00171	0.00182
Total LDL cholesterol	0.00018	0.00022	0.00024	0.00026	0.00028
Total HDL cholesterol	0.00064	0.00076	0.00085	0.00092	0.00098
BMI	0.00592	0.0070	0.00784	0.00851	0.00909
Leptin	0.00133	0.0016	0.00177	0.00192	0.00205
Leptin adjusted for BMI	0.00011	0.00013	0.000143	0.00016	0.00017
CRP	0.00214	0.00254	0.00284	0.00308	0.00329
Ischemic stroke	0.00075	0.00089	0.00099	0.00108	0.00115

Supplementary Table 5: A. PRS results for ↓WS depression (n=10,142) vs. healthy controls (n=8,000) (including bipolar disorder and/or schizophrenia cases, the results were similar when excluding these groups, see Supplementary Figure 4). **B.** Nagelkerke R2 is the reported on the liability scale according to different possible values of ↓WS depression prevalence in the population. Significant results are in bold.

A

Trait	Best p threshold	Beta (SE)	P	OR (95% CI)
Major depressive disorder	0.3	0.18 (0.01)	1.95e-62**	1.20 (1.17-1.23)
Bipolar disorder	0.3	0.10 (0.01)	8.66e-20**	1.11 (1.08-1.13)
Schizophrenia	0.5	0.13 (0.01)	2.66e-32**	1.14 (1.12-1.17)
Anxiety disorders	0.5	0.06 (0.01)	1.07e-08**	1.06 (1.04-1.09)
Alcohol dependence	0.5	0.06 (0.01)	2.22e-08**	1.07 (1.04-1.09)
PTSD	0.4	0.03 (0.01)	1.66e-03*	1.04 (1.01-1.06)
Anorexia nervosa	1	0.10 (0.01)	2.13e-22**	1.11 (1.09-1.13)
Alcohol daily use	5e-8	-0.0090 (0.01)	0.40	0.99 (0.97-1.01)
N cigarettes per day	1	0.03 (0.01)	0.01*	1.03 (1.01-1.05)
Cannabis use lifetime	1	0.04 (0.01)	1.24e-03*	1.04 (1.01-1.06)
Extraversion	0.01	-0.02 (0.01)	0.02*	0.98 (0.96-1.00)
Neuroticism	0.2	0.06 (0.01)	2.50e-07**	1.06 (1.03-1.08)
Type 2 diabetes	1e-5	-0.02 (0.01)	0.05	0.98 (0.96-1.00)
Coronary artery disease	0.01	0.04 (0.01)	3.65e-05**	1.05 (1.02-1.07)
Triglycerides	0.5	0.04 (0.01)	9.20e-04*	1.04 (1.01-1.06)
Total LDL cholesterol	0.001	0.02 (0.01)	0.02*	1.02 (1.00-1.05)
Total HDL cholesterol	0.1	-0.02 (0.01)	0.16	0.98 (0.96-1.01)
BMI	1e-5	-0.04 (0.01)	1.24e-04*	0.96 (0.94-0.98)
Leptin	1e-5	-0.02 (0.01)	0.11	0.98 (0.96-1.00)
Leptin adjusted for BMI	1e-5	0.02 (0.01)	0.16	1.02 (0.99-1.04)
CRP	0.5	0.02 (0.01)	0.16	1.02 (0.99-1.04)
Ischemic stroke	0.001	0.02 (0.01)	0.03*	1.02 (1.00-1.05)

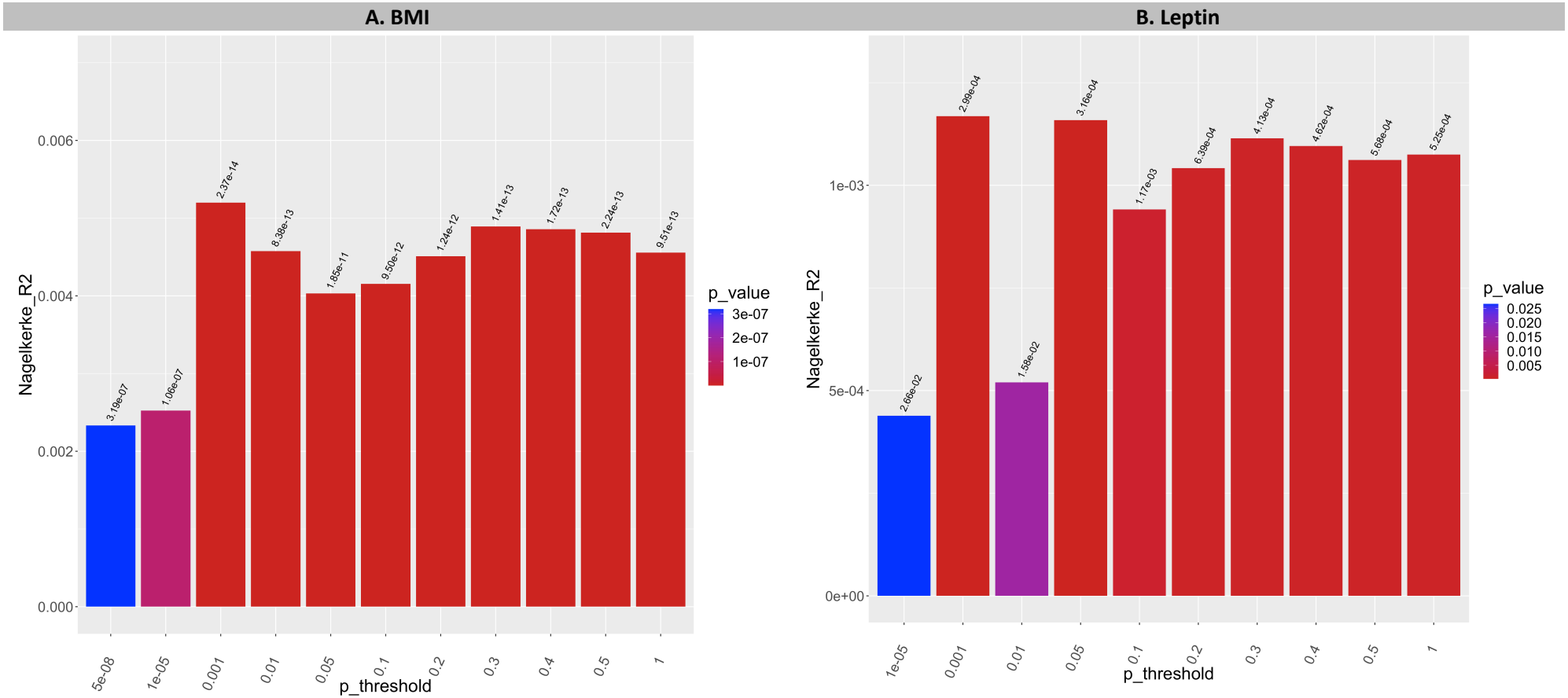
* $p < 0.05$; ** $p < 2.1e-04$

B

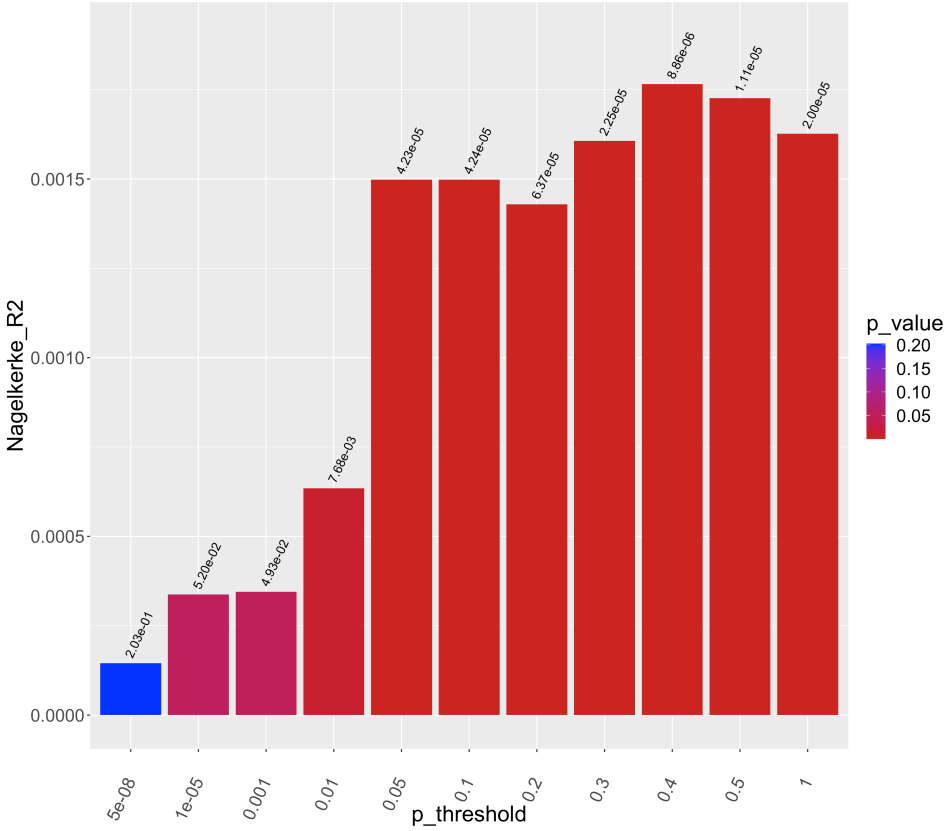
Trait	K=0.03	K=0.04	K=0.05	K=0.06	K=0.07
Major depressive disorder	0.00584	0.00634	0.00677	0.00715	0.00749
Bipolar disorder	0.00173	0.00188	0.00201	0.00212	0.00223
Schizophrenia	0.00293	0.00318	0.00340	0.00359	0.00377
Anxiety disorders	0.00068	0.00074	0.00079	0.00084	0.00087
Alcohol dependence	0.00065	0.00071	0.00076	0.00080	0.00084
PTSD	0.00021	0.00022	0.00024	0.00025	0.00026
Anorexia nervosa	0.00195	0.00212	0.00226	0.00239	0.00251

Alcohol daily use	1.49e-05	1.62e-05	1.73e-05	1.83e-05	1.92e-05
N cigarettes per day	0.00012	0.00014	0.00014	0.00015	0.00016
Cannabis use lifetime	0.00022	0.00024	0.00025	0.00027	0.00028
Extraversion	0.00011	0.00012	0.00013	0.00013	0.00014
Neuroticism	0.00056	0.00060	0.00064	0.00068	0.00071
Type 2 diabetes	8.19e-05	8.89e-05	9.50e-05	1.0e-04	1.05e-04
Coronary artery disease	0.00036	0.00039	0.00041	0.00044	0.00046
Triglycerides	0.00023	0.00025	0.00027	0.00028	0.00029
Total LDL cholesterol	0.00011	0.00012	0.00013	0.00013	0.00014
Total HDL cholesterol	4.15e-05	4.51e-05	4.82e-05	5.09e-05	5.34e-05
BMI	0.00031	0.00033	0.00036	0.00038	0.00040
Leptin	5.22e-05	5.66e-05	6.05e-05	6.39e-05	6.71e-05
Leptin adjusted for BMI	4.08e-05	4.43e-05	4.73e-05	5.00e-05	5.25e-05
CRP	4.15e-05	4.51e-05	4.81e-05	5.08e-05	5.33e-05
Ischemic stroke	0.00010	0.00011	0.00012	0.00013	0.00013

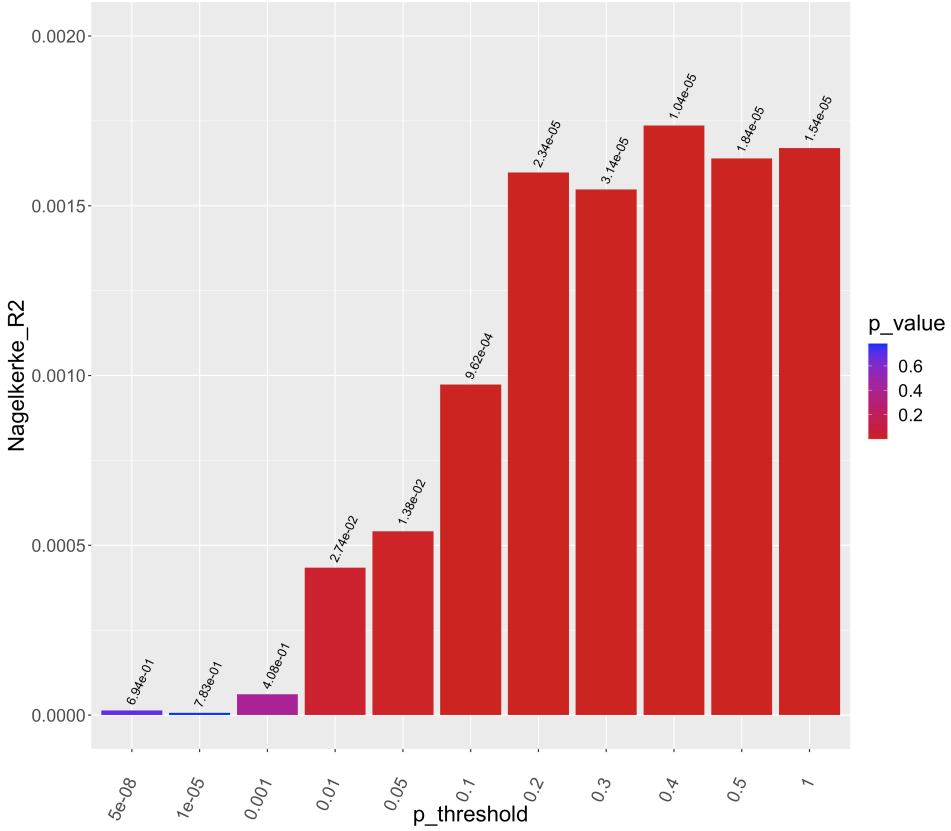
Supplementary Figure 1: barplots representing the results (p-values and Nagelkerke R^2) obtained at the different P_T for the PRS of traits associated with ↑WS depression vs. depression without ↑WS (leptin was very close to the Bonferroni corrected p threshold, the other PRS were statistically significant after Bonferroni correction, see Table 1). Nagelkerke R^2 was reported on the observed scale, since these comparisons included cases only. **A.** BMI; **B.** Leptin; **C.** C-reactive protein (CRP); **D.** Daily alcohol use; **E.** Major depressive disorder.

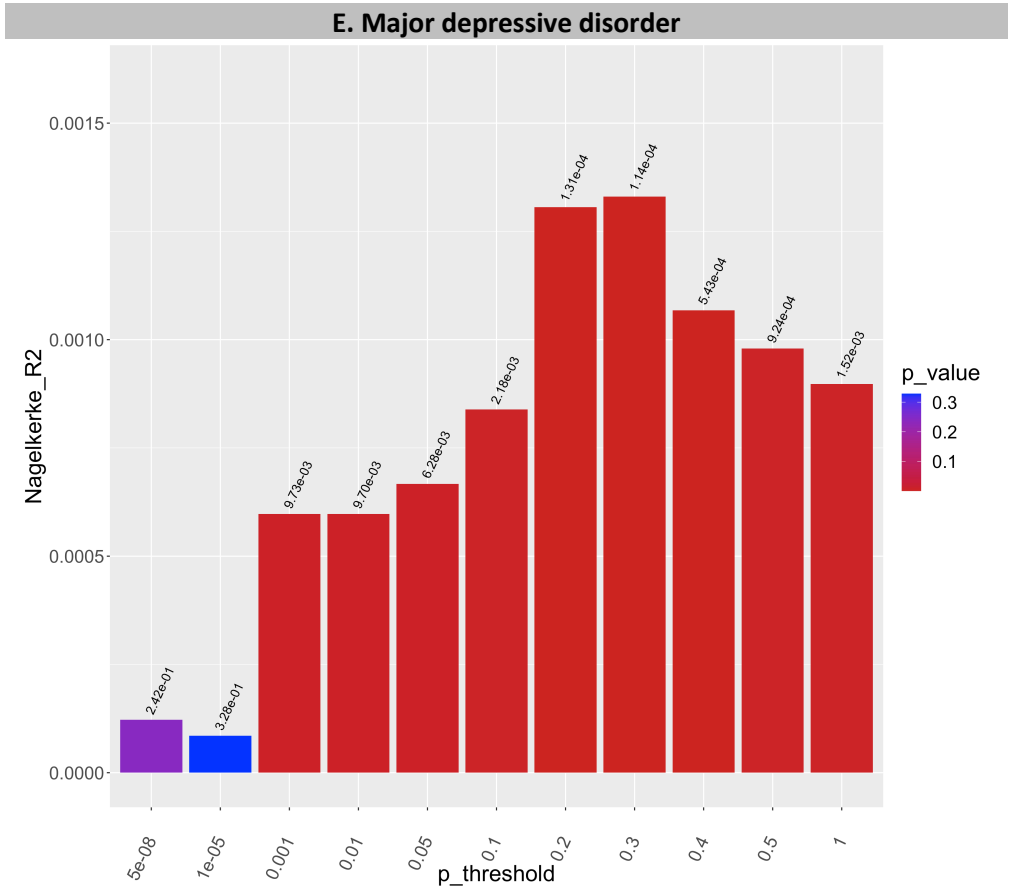


C. C-reactive protein (CRP)

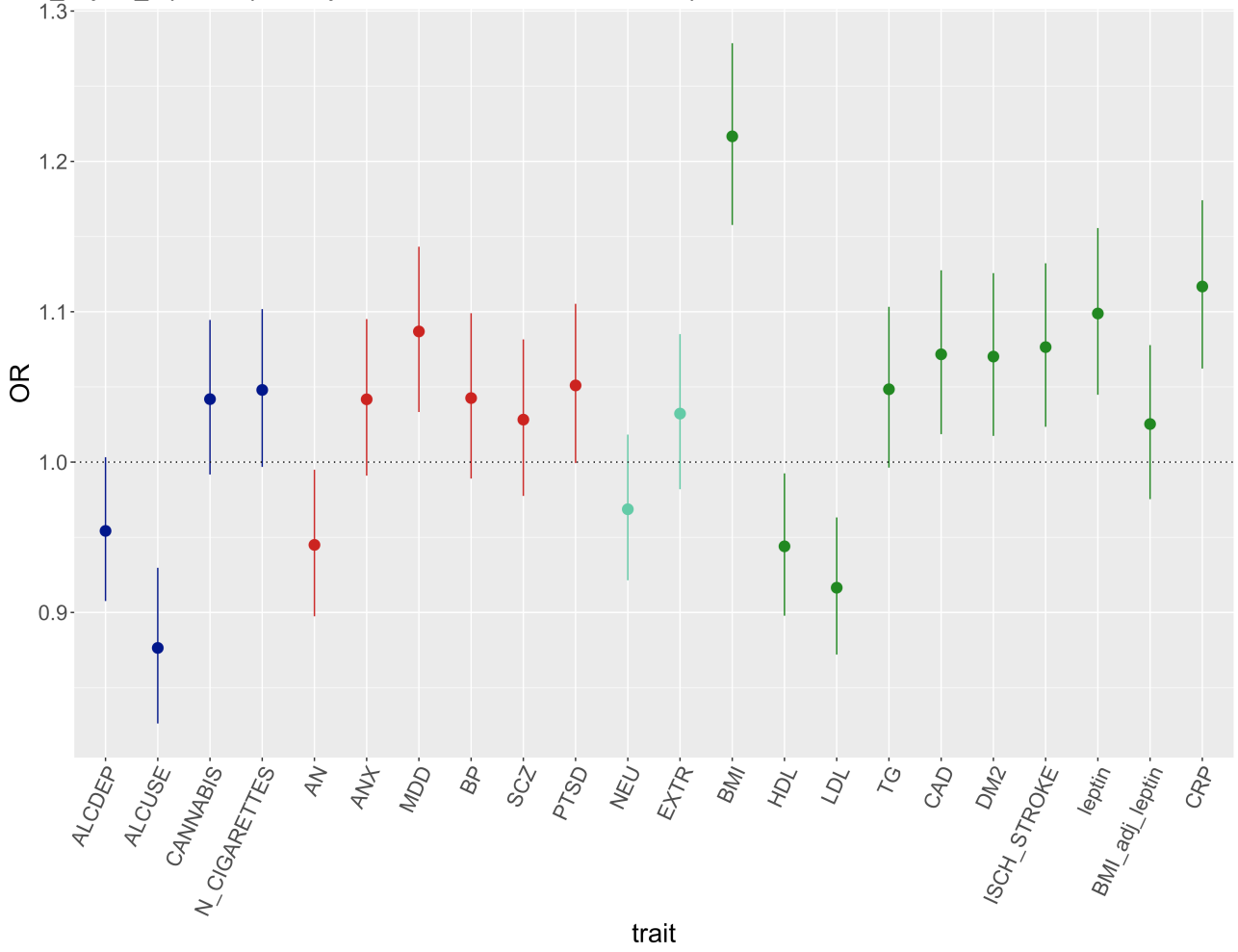


D. Daily alcohol use

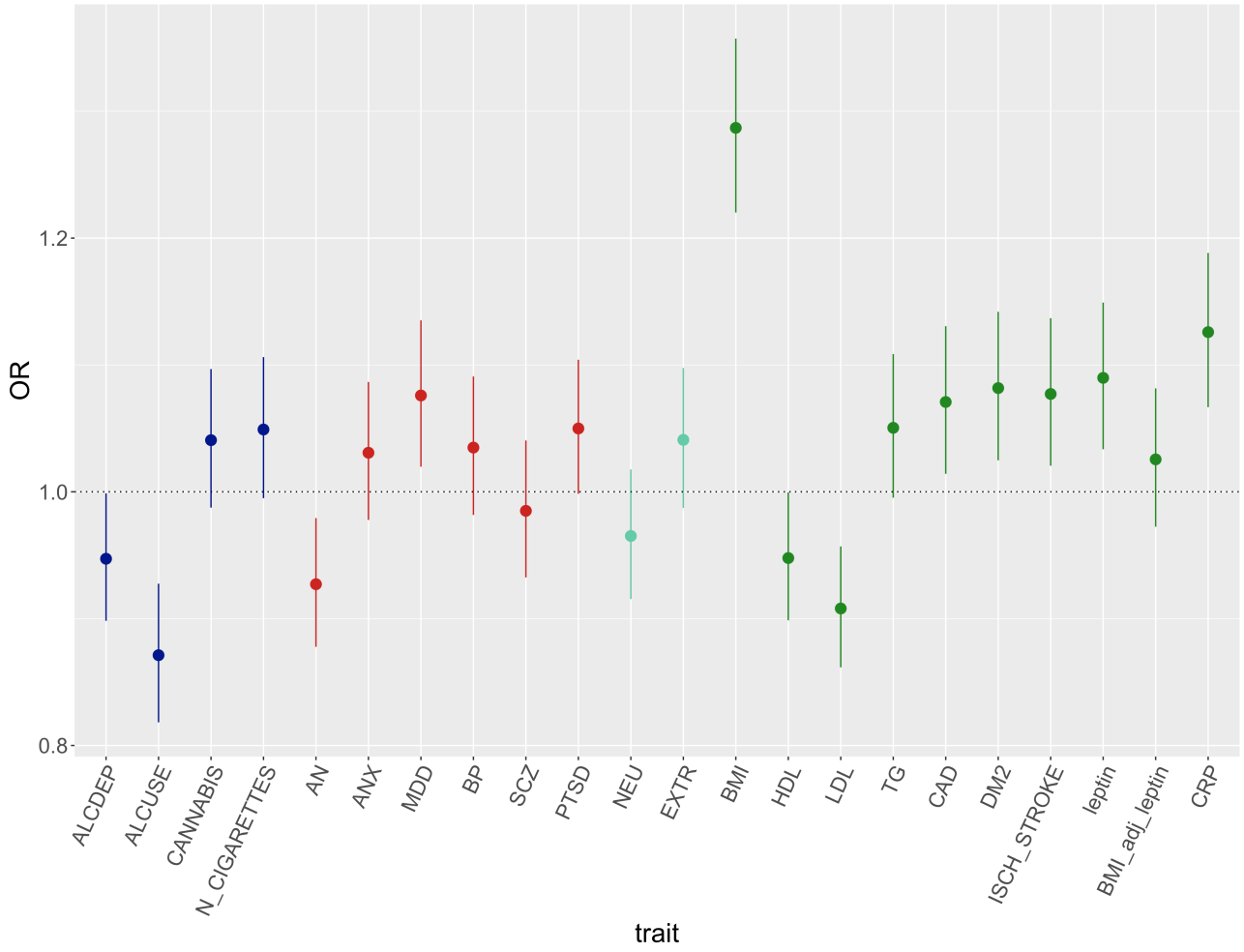



E. Major depressive disorder
Nagelkerke_R2
0.0015
0.0010
0.0005
0.0000
2.42e-01
3.28e-01
9.73e-03
9.70e-03
6.28e-03
2.19e-03
1.31e-04
1.14e-04
5.43e-04
9.24e-04
1.52e-03
p_value
0.3
0.2
0.1
5e-08
1e-05
0.001
0.01
0.05
0.1
0.2
0.3
0.4
0.5
1
p_threshold

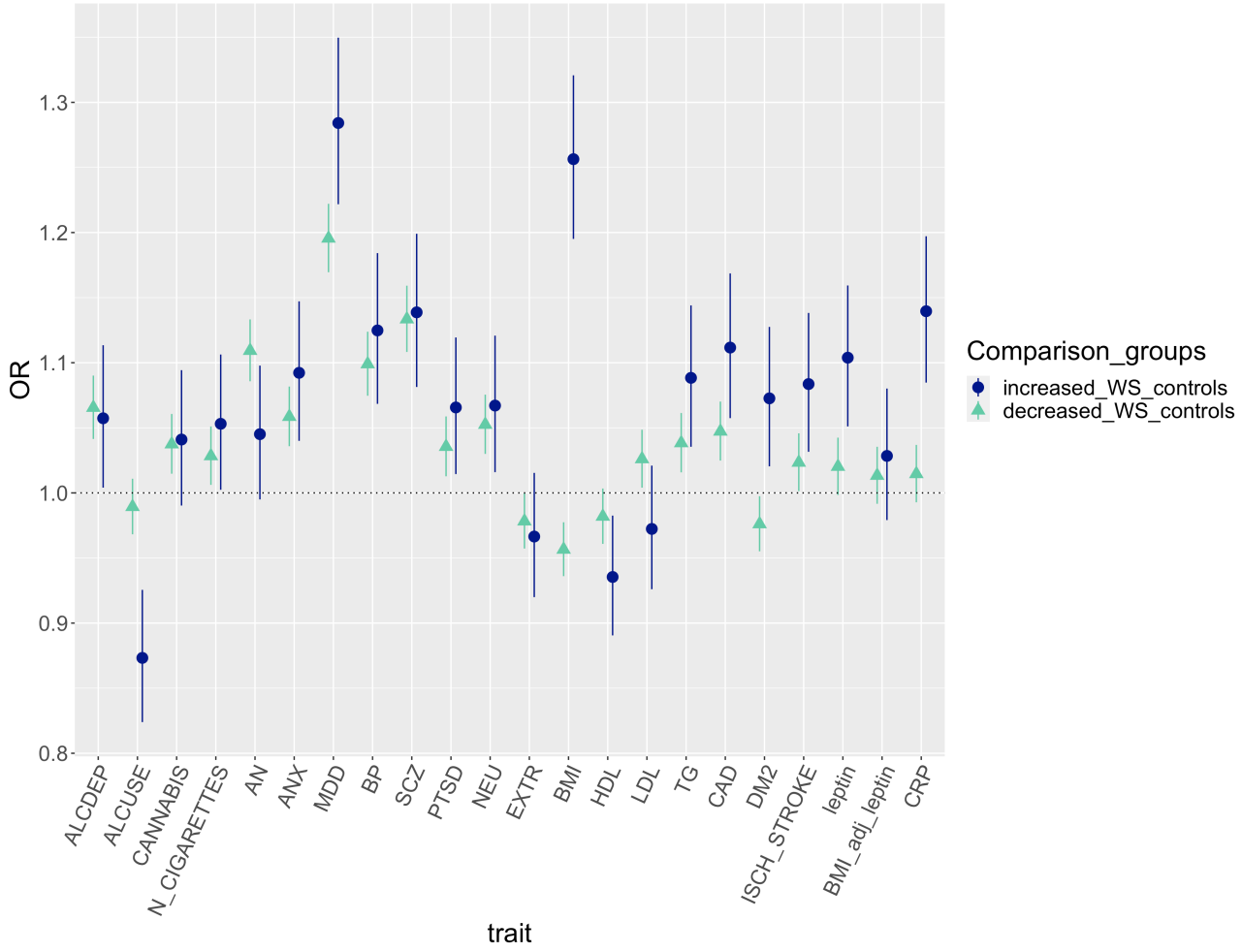
Supplementary Figure 2: PRS odds ratio (OR) and 95% confidence intervals of ↑WS depression vs. non-↑WS depression after excluding people with probable bipolar disorder or schizophrenia or missing information for these variables. None of the results was significantly different compared to what observed in the main analysis. Colors indicate different groups of traits (substance related disorders, major psychiatric disorders, personality traits, immune metabolic traits). BP=bipolar disorder; SCZ=schizophrenia; ANX=anxiety disorders; PTSD=post-traumatic stress disorder; AN=anorexia nervosa; ALCDEP=alcohol dependence; ALCUSE=daily alcohol use; N_CIGARETTES=n cigarettes per day; CANN=cannabis use lifetime; EXTR=extraversion; NEU=neuroticism; DM2=type 2 diabetes mellitus; CAD=coronary artery disease; ISCH_STROKE=ischemic stroke; TG=triglycerides; LDL=total LDL cholesterol; HDL=total HDL cholesterol; BMI=body max index; BMI_adjust_leptin=leptin adjusted for BMI; CRP=C-reactive protein.



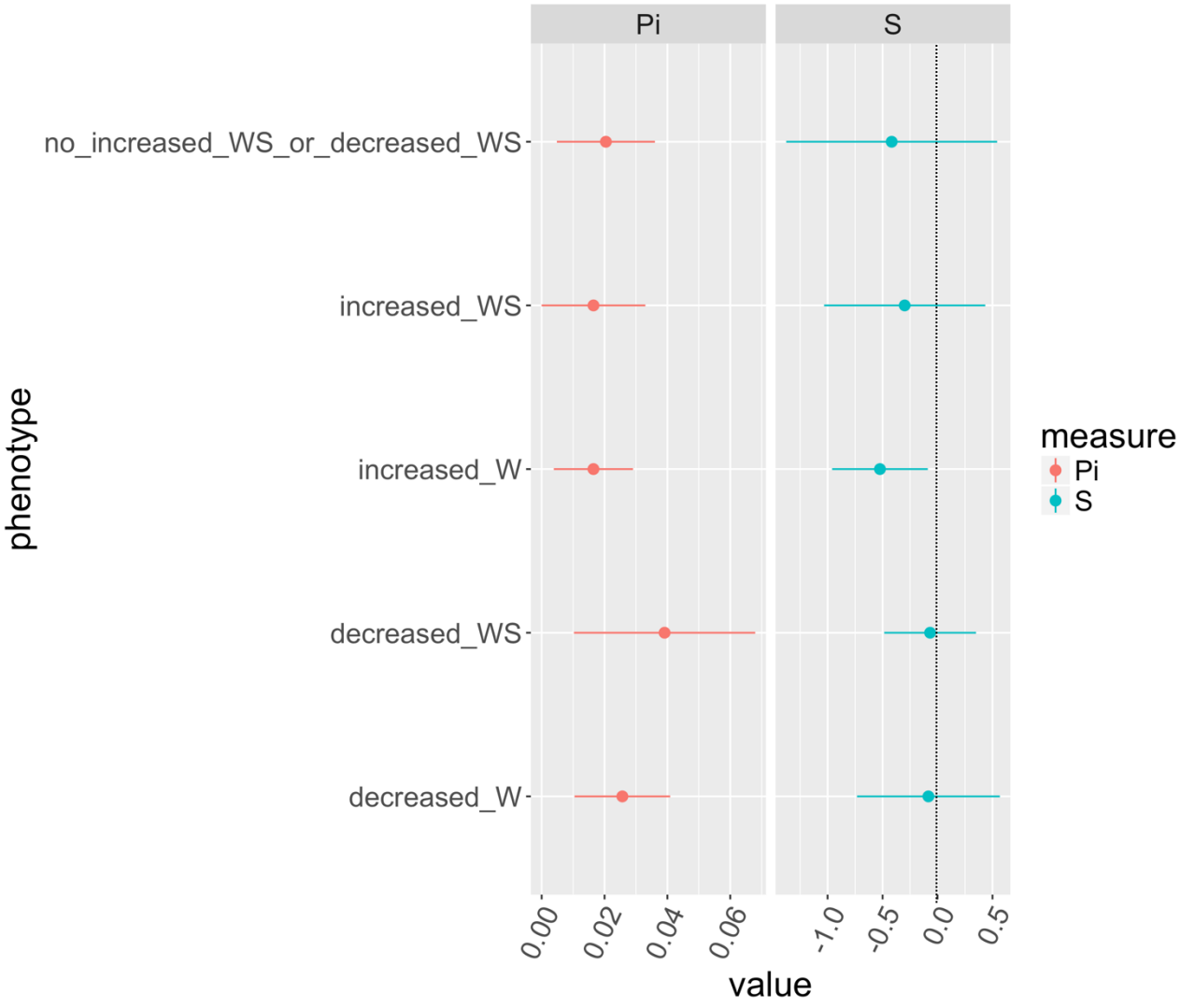
Supplementary Figure 3: PRS odds ratio (OR) and 95% confidence intervals of ↑WS depression vs. ↓WS depression after excluding people with probable bipolar disorder or schizophrenia or missing information for these variables. None of the results was significantly different compared to what observed in the main analysis. Colors indicate different groups of traits (substance related disorders, major psychiatric disorders, personality traits, immune metabolic traits). BP=bipolar disorder; SCZ=schizophrenia; ANX=anxiety disorders; PTSD=post-traumatic stress disorder; AN=anorexia nervosa; ALCDEP=alcohol dependence; ALCUSE=daily alcohol use; N_CIGARETTES=n cigarettes per day; CANN=cannabis use lifetime; EXTR=extraversion; NEU=neuroticism; DM2=type 2 diabetes mellitus; CAD=coronary artery disease; ISCH_STROKE=ischemic stroke; TG=triglycerides; LDL=total LDL cholesterol; HDL=total HDL cholesterol; BMI=body max index; BMI_adjust_leptin=leptin adjusted for BMI; CRP=C-reactive protein.



Supplementary Figure 4: PRS odds ratio (OR) and 95% confidence intervals of ↑WS depression and ↓WS depression vs. healthy controls after excluding people with probable bipolar disorder or schizophrenia or missing information for these variables. None of the results was significantly different compared to what observed in the main analysis. BP=bipolar disorder; SCZ=schizophrenia; ANX=anxiety disorders; PTSD=post-traumatic stress disorder; AN=anorexia nervosa; ALCDEP=alcohol dependence; ALCUSE=daily alcohol use; N_CIGARETTES=n cigarettes per day; CANN=cannabis use lifetime; EXTR=extraversion; NEU=neuroticism; DM2=type 2 diabetes mellitus; CAD=coronary artery disease; ISCH_STROKE=ischemic stroke; TG=triglycerides; LDL=total LDL cholesterol; HDL=total HDL cholesterol; BMI=body max index; BMI_adjust_leptin=leptin adjusted for BMI; CRP=C-reactive protein.



Supplementary Figure 5: estimate and 95% confidence intervals calculated by GCTB-Bayes S for S and Pi parameters. S reflects the correlation between minor allele frequency and SNP effect size, negative values are suggestive of negative natural selection; no depression subtype had S significantly different from zero after multiple-testing correction though depression with weight increase showed a S nominally significantly different from zero (p=0.018). Pi is the proportion of SNPs with non-zero effects. WS=weight and sleep.



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