Else Kröner Fresenius Forschungskolleg „Translationale Psychiatrie“

Age at onset characteristics of bipolar disorder in a cohort of 13,000 patients

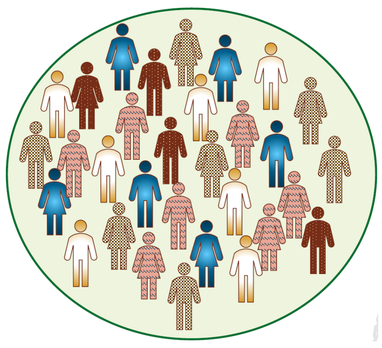
Janos L. Kalman[1,2,3 *], Loes Olde Loohuis[4*], Till F.M. Andlauer[5*], Eli Stahl[6], Mikael Landen[7], Tim Bigdeli[8], Andrew McQuillin[9], Andreas Forstner[10], Douglas Ruderfer[11], Martin Alda[12], Joanna M. Biernacka, Roel Ophoff[4], Thomas G. Schulze[1] (*Affiliations*)

Janos Kalman

Introduction

Early age at onset (AAO) is associated with an unfavourable clinical outcome. Patients with an early AAO may constitute a clinically and biologically homogenous subgroup within the bipolar disorder (BD) spectrum. BD and schizophrenia (SCZ) multiplex families can show a high number of early AAO cases, suggesting a genetic contribution to early AAO. Previous GWAS did not identify AAO-associated variants for BD, indicating that larger samples and a more accurately defined AAO phenotype are required for the detection of AAO-associated common variants. Thanks to the long-standing effort of numerous international investigators, reliable information on AAO is now available for thousands of BD patients, which provides good momentum for investigating the genetic architecture of this phenotype.

The Phenotype



N=12977
N_{BD1}=11236
N_{BD2}=1368
34 cohorts, 18 countriesAAO Definitions

- Earliest age treatment was sought / subjective distress (OPCRIT)
- First met DSM-IV criteria (DIGS, SCID)
- First hospitalization
- First medication

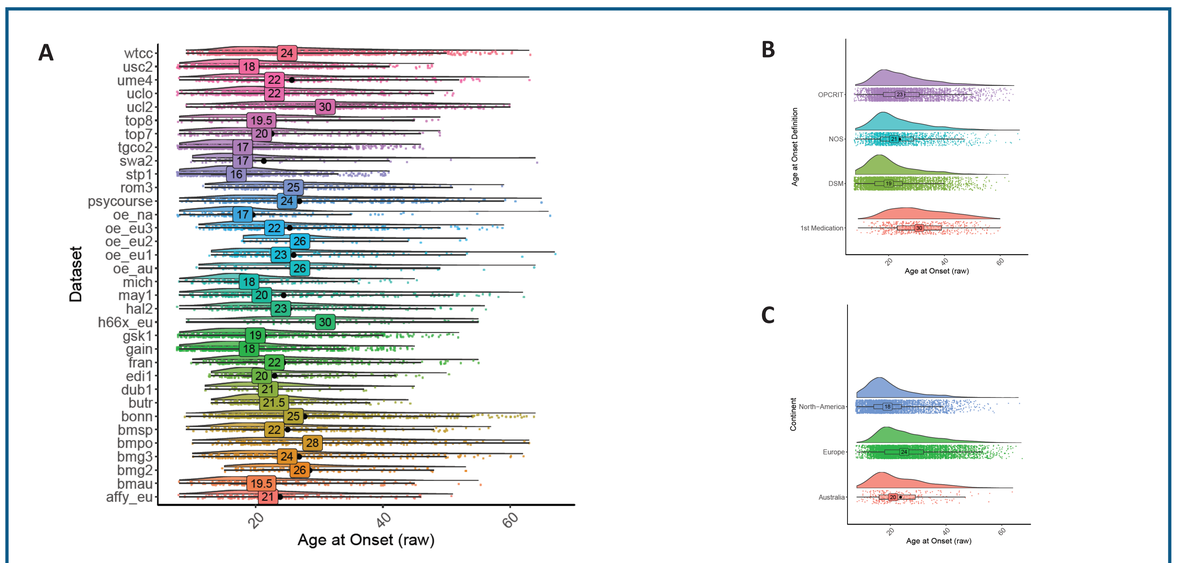


Figure 1. Age at Onset (AAO) differed significantly across the 34 cohorts. (**A**) AAO has been defined, depending on the cohort, as 1) the age at which the proband first met DSM-IV criteria for BD (N=6186, median AAO: 19) 2) the earliest age at which psychiatric treatment was sought or when symptoms began to cause subjective distress or impaired functioning (N=4400, median AAO: 23), 3) the age at first medication (N=609, median AAO: 30), or 4) as a not further specified AAO (N=2516, median AAO: 22). (**B**) Median AAO differed significantly regarding the definition of AAO, (**C**) the continent of origin (North America: 18, Australia: 20, Europe: 24), and the sub-diagnosis (BD-I: 21, BD-II: 22).

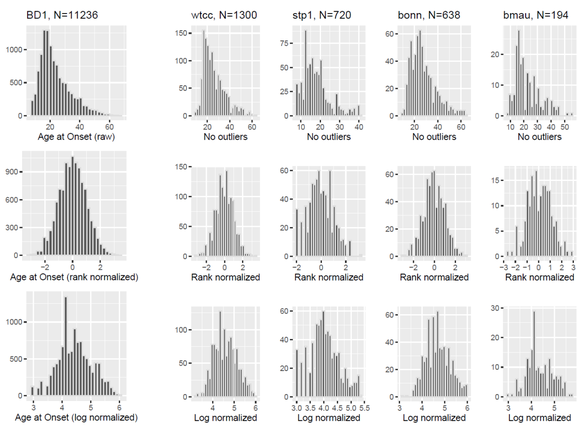
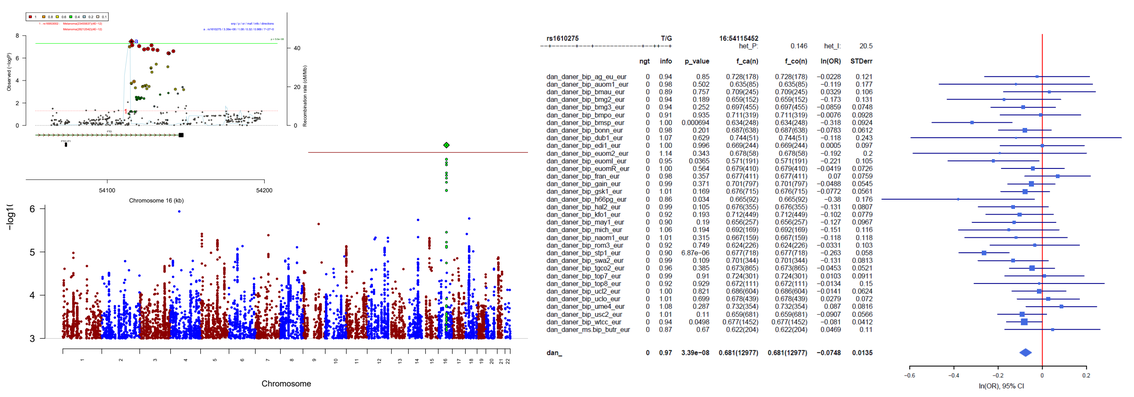


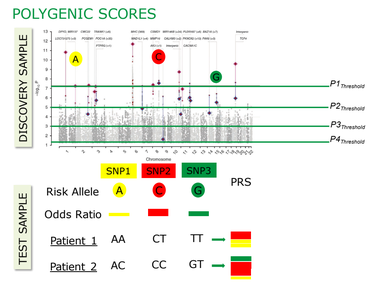
Figure 2. To control for these differences data was normalized within each dataset using inverse rank normalization.

GWAS



As a primary analysis a GWAS of AAO were conducted In each individual cohort. Diagnosis, sex and eight ancestry components were used as covariates. This was followed by an inverse variance-weighted fixed effects meta-analysis.
A locus on CHR16 was associated with AAO at a genome wide significant level (p=3.30e−08, log(OR)=-0,2676).

Polygenic Risc-Scores



The genetic characterizations of AAO and related phenotypes were refined using polygenic risk scores (PRS) for psychiatric disorders and related traits. PRS were calculated after linkage disequilibrium (LD) pruning of GWAS summary statistics on imputed dosage data as described previously (Andlauer et al., Mol Psych 2019). PRS were calculated for SCZ (Fig. 4), BD (Fig. 5), Major Depression (Fig. 6), Attention Deficit Hyperactivity Disorder (ADHD) (Fig. 7), Autism Spectrum Disorder (Fig. 8) and Educational Attainment (Fig. 9) using publicly available summary statistics as training set. Covariates used in the analyses were diagnosis, sex and eight ancestry components. We observed significant, inverse correlation between SCZ, MD, ASD and Educational Attainment PRS and AAO in BD at pT 0.05.

Cohort	N	Beta	SE	R2 (PRS)	p (one−sided)	SW (p)	BP (p)	Q (p)
affy_eu	178	5.595	1.892	0.036	0.99822	0.00	0.01	
bmau	245	−1.404	1.549	0.003	0.18273	0.00	0.08	
bmg2	152	−2.200	2.510	0.005	0.19111	0.00	0.03	
bmg3	455	−3.504	1.449	0.012	0.00800	0.00	0.17	
bmpo	319	−2.668	1.837	0.006	0.07371	0.00	0.42	
bmsp	248	−1.933	1.954	0.004	0.16172	0.00	0.96	
bonn	638	−2.878	1.180	0.009	0.00751	0.00	0.46	
butr	204	−1.327	1.243	0.006	0.14353	0.00	0.66	
dub1	51	−2.061	2.546	0.014	0.21152	0.01	0.92	
edi1	244	1.328	1.319	0.004	0.84250	0.00	0.78	
fran	411	−3.415	1.397	0.014	0.00747	0.00	0.22	
gain	797	0.110	0.743	0.000	0.55868	0.00	0.14	
gsk1	715	−0.584	0.900	0.001	0.25826	0.00	0.77	
h66x_eu	92	−1.982	3.368	0.004	0.27896	0.00	0.48	
hal2	355	−0.380	1.397	0.000	0.39299	0.00	0.41	
may1	257	0.725	2.012	0.001	0.64053	0.00	0.76	
mich	169	−2.818	1.531	0.020	0.03379	0.00	0.40	
oe_au	85	3.669	3.105	0.015	0.87944	0.00	0.95	
oe_eu1	191	−3.770	2.501	0.011	0.06678	0.00	0.10	
oe_eu2	58	−2.783	4.596	0.005	0.27392	0.01	0.54	
oe_eu3	410	−1.624	1.429	0.003	0.12818	0.00	0.61	
oe_na	159	−3.720	2.215	0.017	0.04762	0.00	0.90	
psycourse	449	−2.411	1.498	0.005	0.05412	0.00	0.11	
rom3	226	−6.825	1.849	0.057	0.00014	0.00	0.02	
stp1	718	0.766	0.704	0.002	0.86153	0.00	1.00	
swa2	344	−6.353	1.803	0.034	0.00024	0.00	0.30	
tgco2	865	1.122	0.737	0.003	0.93584	0.00	0.32	
top7	301	−2.674	1.380	0.012	0.02682	0.00	0.18	
top8	111	−3.020	2.465	0.014	0.11171	0.00	0.09	
ucl2	604	−1.740	1.200	0.003	0.07375	0.00	0.17	
uclo	439	−1.392	1.115	0.003	0.10620	0.00	0.77	
ume4	354	−0.848	1.671	0.001	0.30597	0.00	0.69	
usc2	681	−0.102	0.811	0.000	0.44983	0.00	0.92	
wtcc	1452	−1.752	0.731	0.004	0.00831	0.00	0.01	
Meta	**12977**	**−0.935**	**0.220**		**1e−05**			**0.000**

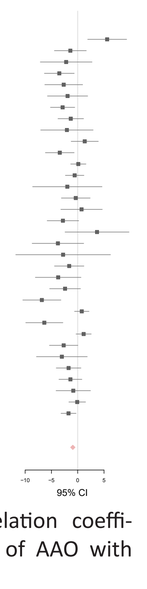


Figure 4. Forest plots with the correlation coefficients and p-values of the association of AAO with **Schizophrenia** PRS at pT=0.05.

Cohort	N	Beta	SE	R2 (PRS)	p (one−sided)	SW (p)	BP (p)	Q (p)
affy_eu	178	1.366	1.424	0.005	0.83053	0.00	0.09	
bmau	245	1.276	1.260	0.004	0.84391	0.00	0.04	
bmg2	152	−2.611	1.588	0.018	0.05124	0.00	0.03	
bmg3	455	−0.371	1.182	0.000	0.62322	0.00	0.48	
bmpo	319	−1.721	1.459	0.004	0.11957	0.00	0.21	
bmsp	248	0.956	1.434	0.002	0.74711	0.00	0.86	
bonn	638	−0.720	1.006	0.001	0.23713	0.00	0.62	
butr	204	−1.150	1.037	0.006	0.13439	0.00	0.65	
dub1	51	−2.750	2.238	0.032	0.11311	0.01	0.86	
edi1	244	−1.732	1.122	0.009	0.06200	0.00	0.47	
fran	411	−1.637	1.134	0.005	0.07490	0.00	0.19	
gain	797	0.536	0.618	0.001	0.80698	0.00	0.13	
gsk1	715	0.372	0.761	0.000	0.68743	0.00	0.69	
h66x_eu	92	0.089	2.584	0.000	0.51376	0.00	0.64	
hal2	355	−2.105	1.131	0.009	0.03175	0.00	0.33	
may1	257	0.975	1.730	0.001	0.71325	0.00	0.92	
mich	169	−2.046	1.322	0.014	0.06181	0.00	0.80	
oe_au	85	2.982	2.518	0.017	0.88000	0.00	0.93	
oe_eu1	191	−2.830	2.029	0.010	0.08248	0.00	0.15	
oe_eu2	58	−5.496	3.240	0.045	0.04824	0.01	0.64	
oe_eu3	410	0.485	1.219	0.000	0.65468	0.00	0.64	
oe_na	159	−0.128	1.751	0.000	0.47089	0.00	0.94	
psycourse	449	−0.985	1.319	0.001	0.22771	0.00	0.09	
rom3	226	1.277	1.539	0.003	0.79614	0.00	0.45	
stp1	718	−0.070	0.602	0.000	0.45356	0.00	0.99	
swa2	344	−3.464	1.682	0.011	0.02012	0.00	0.82	
tgco2	865	0.822	0.623	0.002	0.90634	0.00	0.21	
top7	301	−1.125	1.178	0.003	0.17011	0.00	0.68	
top8	111	2.557	1.979	0.015	0.90034	0.00	0.11	
ucl2	604	0.388	1.088	0.000	0.63913	0.00	0.28	
uclo	439	−2.918	0.907	0.023	0.00069	0.00	0.75	
ume4	354	−0.304	1.371	0.000	0.41223	0.00	0.51	
usc2	681	0.944	0.666	0.003	0.92151	0.00	0.77	
wtcc	1452	−0.364	0.577	0.000	0.26406	0.00	0.51	
Meta	**12977**	**−0.248**	**0.183**		**0.08714**			**0.039**

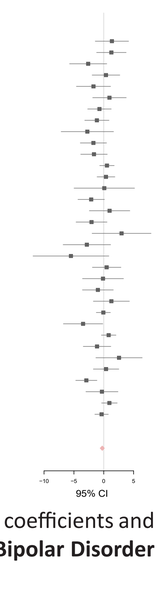


Figure 5. Forest plots with the correlation coefficients and p-values of the association of AAO with **Bipolar Disorder** PRS at pT=0.05.

Cohort	N	Beta	SE	R2 (PRS)	p (one−sided)	SW (p)	BP (p)	Q (p)
affy_eu	178	0.704	4.769	0.000	0.55862	0.00	0.07	
bmau	245	−3.248	4.180	0.002	0.21895	0.00	0.07	
bmg2	152	−4.631	5.206	0.005	0.18760	0.00	0.01	
bmg3	455	−5.302	3.417	0.005	0.06075	0.00	0.45	
bmpo	319	0.105	4.332	0.000	0.50968	0.00	0.13	
bmsp	248	−6.045	4.493	0.007	0.08988	0.00	0.89	
bonn	638	2.023	2.857	0.001	0.76044	0.00	0.63	
butr	204	−0.022	2.887	0.000	0.49692	0.00	0.59	
dub1	51	−4.701	7.358	0.009	0.26322	0.03	0.86	
edi1	244	−0.747	3.055	0.000	0.40354	0.00	0.77	
fran	411	−3.730	3.149	0.003	0.11848	0.00	0.20	
gain	797	−3.214	1.868	0.004	0.04284	0.00	0.12	
gsk1	715	−2.438	2.298	0.002	0.14461	0.00	0.66	
h66x_eu	92	1.783	8.070	0.001	0.58717	0.00	0.65	
hal2	355	0.416	3.598	0.000	0.54593	0.00	0.39	
may1	257	−0.820	4.806	0.000	0.43233	0.00	0.93	
mich	169	0.502	3.881	0.000	0.55138	0.00	0.63	
oe_au	85	−9.587	8.052	0.017	0.11880	0.00	0.96	
oe_eu1	191	3.477	5.931	0.002	0.72079	0.00	0.15	
oe_eu2	58	0.125	9.661	0.000	0.50512	0.01	0.81	
oe_eu3	410	1.582	3.404	0.001	0.67881	0.00	0.52	
oe_na	159	0.392	5.427	0.000	0.52874	0.00	0.88	
psycourse	449	−4.008	3.719	0.002	0.14090	0.00	0.05	
rom3	226	−4.353	4.610	0.004	0.17303	0.00	0.05	
stp1	718	−3.566	1.807	0.005	0.02442	0.00	0.97	
swa2	344	−5.618	4.449	0.005	0.10379	0.00	0.97	
tgco2	865	−3.530	1.791	0.004	0.02457	0.00	0.18	
top7	301	−2.418	3.696	0.001	0.25680	0.00	0.67	
top8	111	1.232	6.073	0.000	0.58020	0.00	0.08	
ucl2	604	−0.601	2.882	0.000	0.41743	0.00	0.25	
uclo	439	−3.467	2.858	0.003	0.11289	0.00	0.78	
ume4	354	2.966	4.325	0.001	0.75332	0.00	0.35	
usc2	681	−2.791	2.133	0.003	0.09556	0.00	0.70	
wtcc	1452	−3.225	1.677	0.003	0.02731	0.00	0.62	
Meta	**12977**	**−2.289**	**0.542**		**1e−05**			**0.996**

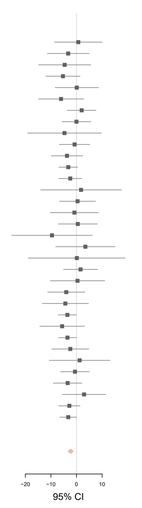


Figure 6. Forest plots with the correlation coefficients and p-values of the association of AAO with **Major Depression** PRS at pT=0.05.

Cohort	N	Beta	SE	R2 (PRS)	p (one−sided)	SW (p)	BP (p)	Q (p)
affy_eu	178	2.216	1.810	0.008	0.88869	0.00	0.10	
bmau	245	−0.937	1.400	0.002	0.25205	0.00	0.06	
bmg2	152	−0.560	2.103	0.000	0.39516	0.00	0.03	
bmg3	455	−0.160	1.275	0.000	0.45013	0.00	0.49	
bmpo	319	2.693	1.579	0.009	0.95544	0.00	0.28	
bmsp	248	−1.392	1.650	0.003	0.19989	0.00	0.94	
bonn	638	0.519	1.059	0.000	0.68777	0.00	0.57	
butr	204	0.287	1.086	0.000	0.60420	0.00	0.66	
dub1	51	0.068	2.786	0.000	0.50972	0.02	0.83	
edi1	244	1.707	1.253	0.008	0.91283	0.00	0.75	
fran	411	2.587	1.179	0.012	0.98563	0.00	0.24	
gain	797	0.428	0.665	0.001	0.74020	0.00	0.09	
gsk1	715	0.524	0.874	0.001	0.72567	0.00	0.64	
h66x_eu	92	−0.922	2.790	0.001	0.37091	0.00	0.61	
hal2	355	1.382	1.341	0.003	0.84830	0.00	0.24	
may1	257	−0.226	1.793	0.000	0.44989	0.00	0.90	
mich	169	−0.069	1.459	0.000	0.48110	0.00	0.75	
oe_au	85	−0.535	3.495	0.000	0.43941	0.00	0.83	
oe_eu1	191	−1.550	2.073	0.003	0.22778	0.00	0.18	
oe_eu2	58	−2.111	3.443	0.007	0.27132	0.01	0.83	
oe_eu3	410	−1.188	1.337	0.002	0.18729	0.00	0.56	
oe_na	159	−0.550	2.012	0.000	0.39250	0.00	0.95	
psycourse	449	−2.067	1.364	0.005	0.06510	0.00	0.09	
rom3	226	0.464	1.656	0.000	0.61027	0.00	0.11	
stp1	718	−0.506	0.665	0.001	0.22330	0.00	0.99	
swa2	344	0.730	1.680	0.001	0.66796	0.00	0.98	
tgco2	865	−0.451	0.697	0.000	0.25894	0.00	0.23	
top7	301	−1.500	1.338	0.004	0.13168	0.00	0.70	
top8	111	−3.660	2.291	0.023	0.05665	0.00	0.12	
ucl2	604	−0.584	1.112	0.000	0.29963	0.00	0.30	
uclo	439	−1.212	1.096	0.003	0.13480	0.00	0.68	
ume4	354	−1.526	1.513	0.003	0.15695	0.00	0.39	
usc2	681	−1.714	0.768	0.007	0.01303	0.00	0.50	
wtcc	1452	−0.022	0.632	0.000	0.48605	0.00	0.48	
Meta	**12977**	**−0.178**	**0.202**		**0.18905**			**0.592**

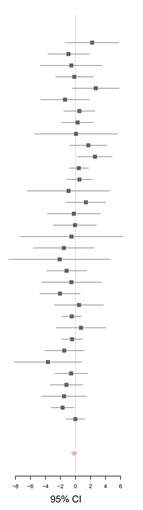


Figure 7. Forest plots with the correlation coefficients and p-values of the association of AAO with **ADHD** PRS at pT=0.05.

Cohort	N	Beta	SE	R2 (PRS)	p (one−sided)	SW (p)	BP (p)	Q (p)
affy_eu	178	3.193	1.678	0.020	0.97063	0.00	0.13	
bmau	245	−2.051	1.357	0.009	0.06606	0.00	0.02	
bmg2	152	−2.310	2.144	0.008	0.14156	0.00	0.01	
bmg3	455	−2.095	1.163	0.007	0.03616	0.00	0.46	
bmpo	319	2.042	1.431	0.006	0.92273	0.00	0.41	
bmsp	248	−1.476	1.598	0.003	0.17840	0.00	0.90	
bonn	638	−0.991	1.064	0.001	0.17594	0.00	0.68	
butr	204	−1.149	1.057	0.006	0.13924	0.00	0.61	
dub1	51	1.360	2.427	0.007	0.71087	0.01	0.79	
edi1	244	−0.472	1.182	0.001	0.34510	0.00	0.77	
fran	411	0.909	1.171	0.001	0.78083	0.00	0.26	
gain	797	−0.885	0.602	0.003	0.07104	0.00	0.12	
gsk1	715	−0.971	0.772	0.002	0.10442	0.00	0.62	
h66x_eu	92	−2.753	2.470	0.013	0.13413	0.01	0.01	
hal2	355	−1.123	1.253	0.002	0.18540	0.00	0.41	
may1	257	1.048	1.624	0.002	0.74031	0.00	0.88	
mich	169	−1.594	1.400	0.007	0.12830	0.00	0.75	
oe_au	85	−1.489	3.196	0.003	0.32128	0.00	0.93	
oe_eu1	191	−0.369	1.889	0.000	0.42262	0.00	0.19	
oe_eu2	58	−2.168	4.406	0.004	0.31249	0.01	0.71	
oe_eu3	410	−0.332	1.224	0.000	0.39327	0.00	0.64	
oe_na	159	0.265	2.005	0.000	0.55246	0.00	0.94	
psycourse	449	−0.798	1.285	0.001	0.26745	0.00	0.14	
rom3	226	0.397	1.596	0.000	0.59802	0.00	0.13	
stp1	718	−1.045	0.651	0.004	0.05432	0.00	0.98	
swa2	344	−0.212	1.467	0.000	0.44260	0.00	0.98	
tgco2	865	−0.188	0.649	0.000	0.38612	0.00	0.26	
top7	301	−1.918	1.198	0.008	0.05524	0.00	0.68	
top8	111	−1.416	2.017	0.004	0.24224	0.00	0.05	
ucl2	604	−0.033	0.981	0.000	0.48671	0.00	0.30	
uclo	439	−0.630	0.972	0.001	0.25840	0.00	0.83	
ume4	354	−1.128	1.459	0.002	0.21992	0.00	0.41	
usc2	681	−0.962	0.709	0.003	0.08765	0.00	0.46	
wtcc	1452	−1.061	0.604	0.002	0.03963	0.00	0.61	
Meta	**12977**	**−0.726**	**0.188**		**6e−05**			**0.924**

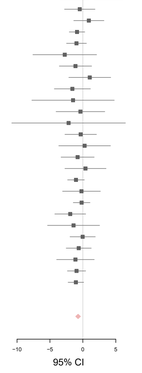


Figure 8. Forest plots with the correlation coefficients and p-values of the association of AAO with **Autism Spectrum Disorder** PRS at pT=0.05.

Cohort	N	Beta	SE	R2 (PRS)	p (one−sided)	SW (p)	BP (p)	Q (p)
affy_eu	178	−3.080	4.149	0.003	0.22943	0.00	0.11	
bmau	245	−2.973	3.263	0.003	0.18160	0.00	0.02	
bmg2	152	0.057	5.008	0.000	0.50456	0.00	0.02	
bmg3	455	0.557	2.850	0.000	0.57751	0.00	0.22	
bmpo	319	−4.537	3.673	0.005	0.10886	0.00	0.33	
bmsp	248	−5.534	3.759	0.009	0.07115	0.00	0.74	
bonn	638	−11.019	2.310	0.035	0.00000	0.00	0.01	
butr	204	4.036	2.541	0.012	0.94307	0.00	0.05	
dub1	51	−6.518	5.766	0.026	0.13244	0.01	0.86	
edi1	244	−4.738	2.585	0.014	0.03402	0.00	0.58	
fran	411	−4.838	2.651	0.008	0.03438	0.00	0.10	
gain	797	0.080	1.495	0.000	0.52139	0.00	0.14	
gsk1	715	−0.862	1.836	0.000	0.31937	0.00	0.60	
h66x_eu	92	2.582	6.541	0.002	0.65294	0.00	0.50	
hal2	355	−1.594	2.827	0.001	0.28662	0.00	0.38	
may1	257	6.792	4.146	0.010	0.94867	0.00	0.90	
mich	169	−1.487	3.170	0.001	0.31981	0.00	0.74	
oe_au	85	2.829	7.745	0.002	0.64200	0.00	0.82	
oe_eu1	191	−1.836	4.861	0.001	0.35308	0.00	0.12	
oe_eu2	58	2.085	9.721	0.001	0.58447	0.00	0.68	
oe_eu3	410	−4.259	2.977	0.005	0.07664	0.00	0.56	
oe_na	159	2.804	3.934	0.003	0.76139	0.00	0.95	
psycourse	449	−3.536	3.195	0.003	0.13450	0.00	0.28	
rom3	226	−0.974	3.524	0.000	0.39124	0.00	0.39	
stp1	718	0.402	1.524	0.000	0.60398	0.00	0.99	
swa2	344	−8.013	3.776	0.013	0.01730	0.00	0.95	
tgco2	865	−1.089	1.604	0.001	0.24861	0.00	0.20	
top7	301	1.052	2.969	0.000	0.63827	0.00	0.67	
top8	111	6.515	5.059	0.014	0.89962	0.00	0.09	
ucl2	604	−3.685	2.396	0.004	0.06227	0.00	0.19	
uclo	439	−1.829	2.376	0.001	0.22098	0.00	0.80	
ume4	354	0.084	3.345	0.000	0.50999	0.00	0.44	
usc2	681	2.762	1.578	0.004	0.95972	0.00	0.88	
wtcc	1452	−1.153	1.445	0.000	0.21255	0.00	0.60	
Meta	**12977**	**−1.185**	**0.449**		**0.00418**			**0.018**

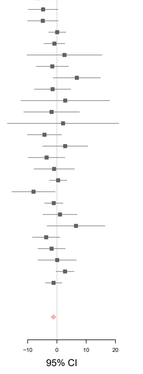


Figure 9. Forest plots with the correlation coefficients and p-values of the association of AAO with **Educational Attainment** PRS at pT=0.05.

Affiliations

[1]Inst. of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich; [2]Dept. of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich; [3]Int. Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich; [4]Center for Neurobehavioral Genetics, Semel Inst. for Neuroscience and Human Behavior, University California Los Angeles; [5]Dept. of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich; [6]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York; [7]Inst. of Neuroscience and Physiology, Dept. of Psychiatry and Neurochemistry, The Sahlgrenska Academy, University of Gothenburg; [8]Department of Psychiatry and Behavioral Sciences, State University of New York Downstate Medical Center; [9]Division of Psychiatry, University College London; [10]Inst. of Human Genetics, University of Bonn; [11]Vanderbilt University Medical Center, Nashville; [12]Dept. of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada; [13]Health Sciences Research, Mayo Clinic, Rochester, Minn.

References

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Summary Outlook

Largest GWAS so far on the AAO phenotype in BD.
Previous studies (Belmonte Mahon et al 2011: 2836 BD, Jamain et al. 2014: 370 early onset (<22y) vs. 2717 controls, Nassan et al. 2016: 600 early onset (<19y) vs. 1811 controls) have all shown negative results.
Collection of additional samples to replicate findings.
Similar analysis on polarity at onset. Additional phenotype-level analyses to gain a better on the genetic and phenotypic background of disease onset in BD.

LMU Ludwig-Maximilians-Universität München
IPPG Institute of Psychiatric Phenomics & Genomics
Max Planck Institute of Psychiatry