**APPENDIX 1**

***Correlation between age at onset (AAO) and year of birth controlling for age at interview***

We used a previously validated procedure to establish the cutoff to be used to select the subsample for the detailed analysis of birth cohort effects[1](#_ENREF_1).

First, we defined strata according to decade of birth and strata and age at interview (categorized into 10 year intervals); then we calculated Spearman’s partial correlation coefficients between AAO and year of birth controlling for the age at interview. As shown in the table below, this approach demonstrated that the correlation between AAO and year of birth remained significant in cases aged <50 years at study entry, even when age at interview was controlled for (Spearman’s r=.13; df 2579; p<0.0001) but that the correlation between AAO and year of birth became non-significant in cases aged >=50 years at study entry (r-=.05; df 1312; p=0.1). Therefore, to minimize the confounding effects of age at interview, we selected those aged>50 years at study entry (n=1274).

Table showing number of cases and correlations between age at onset of bipolar I disorder and birth cohort controlling for age at interview

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Birth cohort | Age at onset in years | | | | | | | | Total |
| <19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70-79 | 80-89 |
| 1910-1919 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 5 |
| 1920-1929 | 0 | 0 | 0 | 0 | 0 | 6 | 52 | 7 | 65 |
| 1930-1939 | 0 | 0 | 0 | 0 | 11 | 195 | 78  *r -.03*  *p=0.72* | 0 | 284 |
| 1940-1949 | 0 | 0 | 0 | 31 | 471 | 177  *r -.07*  *p=0.17* | 0 | 0 | 679 |
| 1950-1959 | 0 | 0 | 27 | 602 | 312  *r .055*  *p=0.12* | 0 | 0 | 0 | 941 |
| 1960-1969 | 0 | 21 | 659 | 406  *r .089*  *p=0.004* | 0 | 0 | 0 | 0 | 1086 |
| 1970-1979 | 3 | 382 | 286  *r .086*  *p= 0.008* | 0 | 0 | 0 | 0 | 0 | 671 |
| 1980-1989 | 34 | 131  *r .128*  *p=0.0035* | 0 | 0 | 0 | 0 | 0 | 0 | 165 |
| Total | 37 | 534 | 972 | 1039 | 794 | 378 | 132 | 10 | 3896 |

Reference :

1. Golmard JL, Scott J, Etain B, et al. Using admixture analysis to examine birth-cohort effects on age at onset of bipolar disorder. Acta Psychiatrica Scandinavica 2016 Mar;133(3):205-213.