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The moderation of the genetic risk for alcohol and drug use disorders in a Swedish national sample by the genetic aptitude for educational attainment

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Abstract

Background.—Does the genetic aptitude for educational attainment (GAEA) moderate the genetic risk for alcohol use disorder (AUD) and drug use disorder (DUD)?

Methods.—In the native Swedish population, born 1960–1980 and followed through 2017 (n = 1 862 435), the family genetic risk score (FGRS) for AUD and DUD and GAEA were calculated from, respectively, the educational attainment and risk for AUD and DUD, of 1st through 5th degree relatives from Swedish national registers. Analyses utilized Aalen's linear hazards models.

Results.—Risk for AUD was robustly predicted by the main effects of $FGRS_{AUD}$ [b = 6.32 (95% CI 6.21–6.43), z = 64.9, p < 0.001) and GAEA [b = −2.90 (2.83–2.97), z = 44.1, p < 0.001] and their interaction [b = −1.93 (1.83–2.03), z = 32.9, p < 0.001]. Results were similar for the prediction of DUD by the main effects of $FGRS_{DUD}$ [b = 4.65 (CI 4.56–4.74), z = 59.4, p < 0.001] and GAEA [−2.08 (2.03–2.13), z = 46.4, p < 0.001] and their interaction [b = −1.58 (1.50–1.66)), z = 30.2, p < 0.001]. The magnitude of the interactions between GAEA and $FGRS_{AUD}$ and $FGRS_{DUD}$ in the prediction of, respectively, AUD and DUD was attenuated only slightly by the addition of educational attainment to the model.

Conclusions and relevance.—The genetic propensity to high educational attainment robustly moderates the genetic risk for both AUD and DUD such that the impact of the genetic liability to AUD and DUD on the risk of illness is substantially attenuated in those with high *v.* low GAEA. This effect is not appreciably mediated by the actual level of educational attainment. These naturalistic findings could form the basis of prevention efforts in high-risk youth.

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Keywords

Alcohol use disorder; drug use disorder; educational attainment; genetics

Using both twin and molecular genetic strategies, we have learned a great deal in recent years about the relationship between the genetic liabilities to major psychiatric and substance use disorders (Consortium, 2013; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; Kendler et al., 2011). We have also begun to clarify the associations between genetic liabilities to our key disorders and genetic propensity for educational attainment (Bulik-Sullivan et al., 2015; Lee et al., 2018; Rosoff, Kaminsky, McIntosh, Smith, & Lohoff, 2020). Considering the genetic aptitude for educational attainment (GAEA) and the genetic risks for alcohol use disorder (AUD) and drug use disorder (DUD), heritability has been shown to be substantial for all three phenotypes from twin models (Baker, Treloar, Reynolds, Heath, & Martin, 1996; Branigan, McCallum, & Freese, 2013; Kendler et al., 2015a; Tambs, Sundet, Magnus, & Berg, 1989; Tsuang et al., 1996; Verhulst, Neale, & Kendler, 2015). High educational attainment, socio-economic status (SES), and intelligence are consistently associated with lower levels of alcohol consumption and/or problematic drinking in Sweden (Sjölund, Hemmingsson, & Allebeck, 2015a; Sjölund, Hemmingsson, Gustafsson, & Allebeck, 2015b; Wennberg, Andersson, & Bohman, 2002; Zettergren & Bergman, 2014), and similar trends are typically seen elsewhere (Barr, Silberg, Dick, & Maes, 2018; Müller et al., 2013; Rogne, Pedersen, & Von Soest, 2021). In two twin studies, the heritability of alcohol consumption was moderated by SES such that heritability was lower in subjects with higher SES (Davis & Slutske, 2018; Hamdi, Krueger, & South, 2015).

We seek to expand on these two twin studies in four important ways. First, we examined AUD rather than alcohol consumption. Second, instead of using an overt measure such as SES, we instead look at the genetic propensity to high educational attainment. This permits us to model directly the interaction at a genetic level, an approach rarely implemented in the past. Third, we added a second substance use disorder, DUD, to see if the findings generalize. Finally, instead of using twin models, we take advantage of a recently developed method to estimate genetic risks or aptitudes from extended pedigrees in a Swedish national sample – the family genetic risk score (FGRS) (Kendler et al., In press; Kendler, Ohlsson, Sundquist, & Sundquist, 2021a, 2021b). So, our specific question is whether the genetic risks for AUD and DUD are moderated by the GAEA. In line with prior work, we predict that, if moderation occurs, high levels of GAEA will attenuate the impact of genetic liability on the risk for AUD or DUD.

Methods

We collected information on individuals from Swedish population-based registers with national coverage linking each person's unique personal identification number, which for confidentiality, was replaced with a serial number by Statistics Sweden. This study was approved by the Regional Ethical Review Board of Lund (No. 2008/409, 2012/795, and 2016/679).

Our database consisted of all individuals born in Sweden from 1960 to 1980 of parents themselves born in Sweden. In the database, we included date of first registration for AUD and DUD utilizing ICD-8, 9, 10 codes from Swedish national primary care, specialist, and hospital registries as well as criminal registers and prescribed drug registers. We also included individual educational attainment (see Appendix Table 1 for full definitions). In the database, individual FGRS for the two disorders as well as a GAEA were included. Similar to prior studies (Kendler et al., In press; Kendler et al., 2021a, 2021b), the FGRS and GAEA were based on selected 1st, 2nd, 3rd, 4th, and 5th degree relatives to the probands with a mean of 40.1 relatives per proband. Briefly (see Appendix Table 2 for details), we first calculated the morbid risk for the phenotype in our sample of relatives based on age at first registration and then we transformed the binary trait into an underlying liability distribution, with the threshold that divides the population into those unaffected and affected for the disorder. Thereafter, we calculated the mean *z*-score for relatives with the disorder and the mean *z*-score for individuals without the disorder. For first-degree relatives, we also multiplied the *z*-score with a factor that sought to subtract the influence of cohabitation separately for siblings and parent–offspring pairs, thereby helping to remove from the FGRS any residual shared-environmental effect. For parent–offspring pairs, this was calculated by comparing the resemblance, by logistic regression, for father–offspring pairs where the biological father sired and raised his child (i.e. a father in an intact family) to the resemblance between children and their not-lived-with fathers, that is, those who sired their off-spring but never lived with or near them when they were growing up. We have examined such not-lived-with fathers in several prior extended adoption studies (e.g. Kendler et al., 2015a 2015b). For sibling pairs, we compared the resemblance in half-sibs who were *v.* were not reared together. As seen in Table 2 step 3 in the Appendix, the correction factors – the degree of the resemblance for our individual diagnoses that was retained after discounting the effect of shared environment equaled 0.99 (AUD) and 0.92 (DUD) for parent–offspring pairs and 0.69 (AUD) and 0.52 (DUD) for sibling pairs. Within each type of relative, we then had two components: the sum of the *z*-score and the total weighted number of relatives. These two components were weighted according to the genetic resemblance to the proband. For each proband, we summed the two components across all groups of relatives and used the quotient between the two components. Finally, to obtain the individual FGRS, we multiplied the quotient with a shrinkage factor based on the variance of the *z*-score across all relatives, the variance in the mean *z*-score across all probands, and the number of weighted number of relatives for each proband. So that the FGRSs would be more comparable across traits and to reduce the effect of register coverage, we standardized the FGRS by year of birth and county of residence into a *z*-score with mean = 0 and S.D. = 1. The calculation for GAEA followed the same principles but was simpler as we summed the weighted (by genetic resemblance) educational attainment across all relatives. The educational attainment was discounted for the effect of shared environment by a factor of 0.82 for parents and 0.73 for siblings. The weighted sum was then further weighted by number of relatives and standardized as described above.

To investigate whether GAEA moderates the impact of the familial genetic risk, we used Aalen's linear hazards model (Aalen, 1989). Follow-up time in months was measured from age 15 until time of first registration for AUD (DUD), death, emigration, or end of

follow-up (31 December 2017). In the first model, aside from year of birth and sex, we include $FGRS_{AUD}$ (DUD) and the GAEA as well as their interaction. The results from this model are presented as the excess number of cases per 10 000 person-years, and the interaction is measured on the additive scale as we have defended previously (Kendler & Gardner, 2010). To investigate the degree to which the interaction is a result of the effect of GAEA on educational attainment, we fitted three additional models, where the follow-up time started at age 25 so as to increase the chance that individuals had largely completed their education. Individuals who were registered for AUD or DUD prior to age 25 were excluded. Model A is the same model as described above, while model B also includes a main effect for educational attainment and model C further includes two additional two-way interaction terms [between educational attainment and $FGRS_{AUD}$ ($FGRS_{DUD}$), and between educational attainment and GAEA] as well as a three-way interaction term between $FGRS_{AUD}$ ($FGRS_{DUD}$), GAEA, and educational attainment. In all models, we investigated the proportionality assumption and there were no major violations. Statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, 2012) and the R-package Timereg in R (Martinussen & Scheike, 2006; Scheike & Zhang, 2011; Team, 2020).

Results

Descriptive statistics

Table 1 provides descriptive statistics for the AUD and DUD. AUD had a modestly higher population prevalence (5.4%) than DUD (3.4%), with the expected male excess in both disorders. In affected individuals, the genetic risk for each of the disorders was more strongly elevated for DUD (+0.72 S.D.) than for AUD (+0.58 S.D.). The average GAEA was substantially below the population mean for individuals affected with DUD (−0.40 S.D.) and AUD (−0.34 S.D.).

Model fitting: primary models

We first predicted risk for AUD controlling for sex and year of birth (Table 2). The model contained both the linear effects of the FGRS for AUD and the GAEA and their interaction. As expected, the FGRS for AUD had a strong and substantial effect on AUD risk while GAEA had a protective effect, approximately half as strong. Most importantly, we found a robust negative interaction between the $FGRS_{AUD}$ and the GAEA (Fig. 1a). For those with a high GAEA [light blue line (very light grey) at the bottom of the figure], the slope of increased risk with increasing $FGRS_{AUD}$ was relatively flat – that is, a large increase in genetic risk produced only a modest increase in affected cases. However, this slope got steeper as the GAEA got lower. At the lowest level of GAEA, the same change in $FGRS_{AUD}$ risk produced more than three times as many affected individuals as seen with those at the highest level of GAEA.

For DUD, both the main effect of the $FGRS_{DUD}$ and the GAEA were slightly smaller than seen with AUD as was the interaction between them (Table 2) but the pattern of their interaction, as illustrated in Fig. 1b, was very similar to that seen for AUD.

Model fitting with educational attainment

GAEA appeared to strongly moderate the impact of the genetic risk for AUD and DUD. However, this moderation by GAEA could be largely driven by the impact of GAEA on educational attainment itself. To investigate this, we fitted three models to our original sample from which we censored individuals with a registration of AUD/DUD prior to <age 25 to insure they had achieved their final level of educational attainment (Table 3). Model A is the same model fitted to our entire sample in Table 2. The results were similar although the strength of the interaction effects between the FGRS and GAEA declined for both AUD and DUD suggesting that these interactions are strongest in the early onset cases censored from this sample.

Model B included a main effect for educational attainment which robustly predicted risk for AUD and DUD. Importantly, the magnitudes of the interaction between GAEA and the $FGRS_{AUD}$, and $FGRS_{DUD}$ observed in this model were nearly identical to those seen in model A. These results indicate that little of the observed interaction between GAEA and the genetic risks for AUD and DUD was mediated through actual educational attainment.

Model C contained all the parameters in model B to which we added a three-way interaction between the relevant FGRS, GAEA, and educational attainment. This interaction was significant for both AUD and DUD. We illustrate this interaction in Fig. 2a and b presenting the results obtained for individuals with high educational attainment (+1 S.D.), mean educational attainment, and very low educational attainment (−2 S.D.). The pattern was similar across both AUD and DUD. The largest interaction between GAEA and FGRS was seen in those with very low educational attainment. The interaction was present but attenuated for those who obtained a mean level of education. However, for those at high educational attainment, the interaction effects disappeared.

Discussion

The goal of this paper was to determine whether the GAEA moderates the impact of the genetic risks for AUD and DUD on rates of, respectively, AUD and DUD. We addressed this question with three analyses. We review them in turn.

First, in a national sample of individuals affected with AUD and DUD, we found, consistent with prior studies of the phenotype of educational attainment (Davis & Slutske, 2018; Hamdi et al., 2015), that high GAEA attenuated the impact of genetic liability on the risk of both AUD and DUD. This effect was clearly seen in the slope of the FGRS curves depicted in Fig. 1. For both AUD and DUD, the slope of the curve was shallowest for those with the highest GAEA and became progressively steeper as the GAEA became lower.

Second, while the Swedish registry does not contain the fine-grained phenotypic assessments that would permit us to test the specific mechanisms through which the GAEA protected against the genetic risk for AUD and DUD, we could evaluate one important hypothesis – the degree to which the protective effect of GAEA results from its impact on the actual level of educational attainment. Contrary to our expectation, our analyses demonstrated that almost none of the moderating effects of GAEA on genetic risk for AUD

and DUD was mediated through the completed years of education. Instead, the resilience to genetic risk for AUD and DUD associated with a high GAEA likely results from the direct effects of GAEA.

We would speculate that the direct protective effect of GAEA on genetic risk for AUD and DUD likely involves its impact on cognition, personality, and development. A number of studies have used twin and molecular-genetic strategies to disentangle the components of the GAEA. Consistent with prior studies (Belsky et al., 2016; Johnson, Deary, & Iacono, 2009; Tambs et al., 1989), Krapohl et al. (2014) found that the strongest component of the heritability of EA is intelligence. That high levels of general cognitive functioning could mediate the protective effect of GAEA in our Swedish sample is supported by a range of studies showing that high IQ in Sweden is related to lower levels of problematic drinking and/or the negative consequences thereof (Müller et al., 2013; Sjolund, Allebeck, & Hemmingsson, 2012; Sjölund et al., 2015a; Zettergren & Bergman, 2014). Other more specific cognitive processes could also be involved in protective effects such as working memory (Ellingson, Fleming, Vergés, Bartholow, & Sher, 2014).

However, Krapohl et al. (2014) also found that substantial proportions of the genetic propensity to high educational attainment resulted from the personality trait of self-efficacy. Other studies have shown that a polygenic risk score (PRS) for educational attainment predicts high levels of conscientiousness, agreeableness (Smith-Woolley, Selzam, & Plomin, 2019), and self-control (Belsky et al., 2016), personality traits which, along with the correlated constructs of self-efficacy and constraint, predict low levels of impulsivity, risk taking, and substance misuse (Belcher, Volkow, Moeller, & Ferre, 2014; Bogg & Roberts, 2004; Kendler et al., 1999; Settles et al., 2012; Tang, Posner, Rothbart, & Volkow, 2015).

Finally, strong academic performance in adolescence, predicted by GAEA, is associated with reduced risks for psychoactive substance use and subsequent AUD and DUD (Fothergill et al., 2008; Gauffin, Vinnerljung, Fridell, Hesse, & Hjern, 2013; Schulenberg, Bachman, O'Malley, & Johnston, 1994). Evidence that this relationship is likely causal comes from individual and school-based interventions for children and adolescents showing that improving academic performance results in lower psychoactive substance use (Eggert, Thompson, Herting, Nicholas, & Dicker, 1994; Fletcher, Bonell, Sorhaindo, & Strange, 2009; Lewis et al., 2012). Furthermore, recent prospective cohort studies employing instrumental variable and co-relative designs have shown that high academic performance was likely causally related to a lowered risk for both DUD (Kendler et al., 2018b) and AUD (Kendler et al., 2020). These findings are consistent with the predictions of social control (Hirschi, 1969) and social development theories (Kellam et al., 2008), which posit that students who succeed academically develop positive attachments to school. These attachments tend to facilitate a commitment to a prosocial lifestyle which in turn reduces the risk for AUD or DUD. By contrast, those who perform poorly in school are more likely to adopt antisocial lifestyles including an elevated risk for AUD and DUD. Thus, high GAEA would predict a developmental pathway marked by academic achievement which leads to the adoption of prosocial attitudes which could protect again the impact of high genetic risk for DUD or AUD.

Our third analysis examined whether the magnitude of the interactions between GAEA and $FGRS_{AUD}$ and $FGRS_{DUD}$ depended on the level of educational attainment. We found a robust three-way interaction which revealed a much stronger moderation of the genetic risk for AUD and DUD by GAEA in individuals with low *v.* high educational attainment. That is, much of the buffering by GAEA of the impact of elevated genetic risk for AUD and DUD in the Swedish population occurs in those with low levels of education. If targeted interventions could be developed on the basis of our findings with the goal of reducing future risk for substance use disorders, such interventions would have the highest impact if directed to those with high familial risk for AUD and/or DUD and low educational attainment.

Limitations

These findings should be viewed in the context of six potential methodological limitations. First, our results are dependent on the quality of the diagnosis of AUD and DUD in Swedish registries. While such registry data have important advantages (e.g. no refusals or reporting biases), it will not identify all the same cases as an interview-based assessment. Our affected subjects are likely, on average, more severely ill than those meeting DSM-5 criteria (American Psychiatric Association, 2013) at interview, although our lifetime prevalence of AUD and DUD is only moderately lower than those identified in nearby Norway (Kringlen, Torgersen, & Cramer, 2001). The validity of our definitions is supported by the high rates of concordance observed across our ascertainment methods (Kendler, Lönn, Salvatore, Sundquist, & Sundquist, 2018a; Kendler et al., 2015a, 2015b). Furthermore, the pattern of resemblance in relatives for AUD and DUD seen in Sweden is similar to those found in other samples based on personal interviews (Prescott & Kendler, 1999; Tsuang et al., 1996).

Second, our FGRS, used previously in this journal (Kendler et al., In press), assesses genetic risk on the basis of the aggregation of disorders in close and distant biological relatives and is not equivalent to a molecular PRS. Our corrections for shared environmental effects with parents and siblings are approximate. We also correct for year of birth to control for possible cohort effects and county of birth control for regional variations in diagnostic or policing practices. Appendix Table 3 shows that our final genetic risk scores are not highly sensitive to key steps in their calculation, as their deletion produces results that correlate highly with those from the full model and have similar predictive power. We show (Appendix Fig. 1) that the FGRS for DUD and AUD is relatively stable across regions within Sweden and have found, when controlling for pedigree structure, that the FGRS correlates very highly with a recently published quantitative family-history score using a different analytic approach (Hujoel, Gazal, Loh, Patterson, & Price, 2020).

We also explored, in several different analyses, the impact of the degree of relatives included in the FGRS calculation. In Appendix Table 4, we show the high correlations in the FGRS reported in the MS for 1st through 5th degree relatives with those obtained by eliminating more distant relatives and in Appendix Table 5, show the polychoric correlation between AUD/DUD and $FGRS_{AUD}$, $FGRS_{DUD}$, and $FGRS_{EDU}$ as a function of the breadth of relatives considered. The results are relatively stable until we trim down to only 1st and 2nd degree relatives. In Table 6, we recalculate our main results with various trimmings of

the classes of relatives considered which shows that our findings are not sensitive to the particular set of relatives that contribute to the FGRS.

Third, as in other samples (Compton, Thomas, Stinson, & Grant, 2007; Kessler et al., 1997), we observe substantial comorbidity between AUD and DUD. We therefore re-ran our key results in four groups: AUD with DUD only cases censored, DUD with AUD cases only censored, AUD with comorbid DUD-AUD cases censored, and DUD with comorbid DUD-AUD cases censored. As seen in Appendix Table 7 and Fig. 2, the broad pattern of moderation seen in our main analyses was evident in all four of these groups.

Fourth, would our findings differ if analyzed with a more standard multiplicative Cox model, rather than the additive model employed? We present the results for AUD and DUD using such a model in Appendix Table 8 and Fig. 3a and b. The same pattern of results is observed.

Fifth, ADHD diagnoses are genetically correlated with risk for substance use disorders (Hicks, Iacono, & McGue, 2012; Kendler & Myers, 2014) and might contribute to their association with GAEA, but were not considered here.

Finally, there is substantial current interest in the relationship of the genetic influences on AUD and alcohol consumption (e.g. Kranzler et al., 2019). While it would therefore be of interest to see if we obtained similar or different results for the interactions of GAEA on genetic control of alcohol consumption as we do for $FGRS_{AUD}$, no registry data are available in Sweden for individual alcohol consumption levels.

Conclusions

The genetic propensity to high educational attainment substantially moderates genetic risk for both AUD and DUD. The impact of the genetic liability to AUD and DUD on the risk of illness is substantially attenuated in those with high *v.* low GAEA. This effect is not appreciably mediated by the level of educational attainment. Rather, it likely arises because individuals with high GAEA tend to have higher levels of intelligence, conscientiousness, self-control, and follow a developmental pathway that includes good school performance leading to prosocial attitudes. All these factors, in aggregate, seem to protect even those at high genetic risk, from developing AUD and DUD. The protective effects of a genetic propensity to high educational attainment on risk for substance use disorders are particularly strong in those with low educational attainment. These naturalistic findings could form the basis of prevention efforts in high-risk youth. Our findings are also of theoretical interest and encourage further investigations, including those using polygenic risks scores, that examine the degree to which genetic liabilities for psychiatric and substance use disorders moderate the impact on one another on disorder risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Access to data and data analysis.

Kristina Sundquist had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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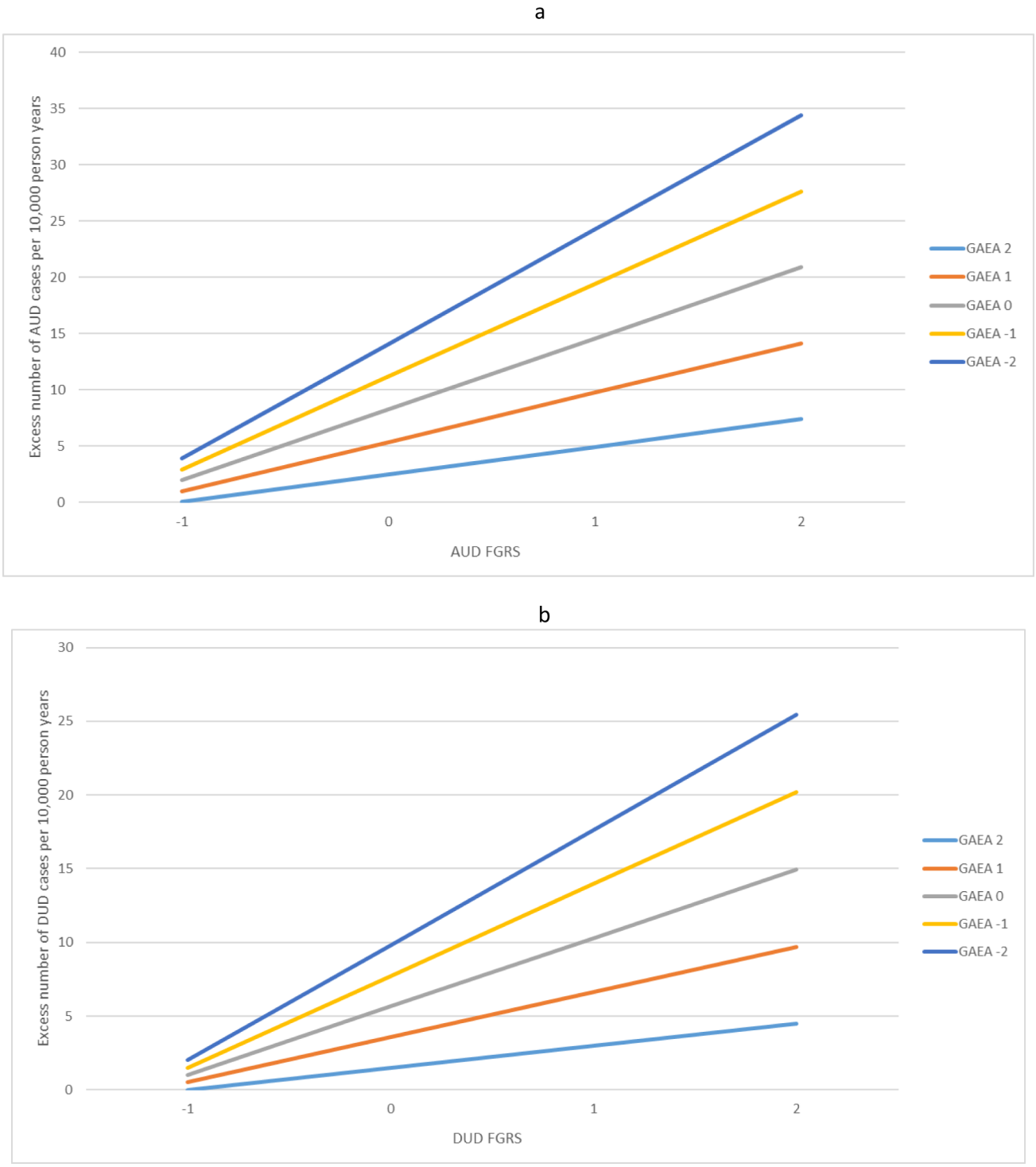
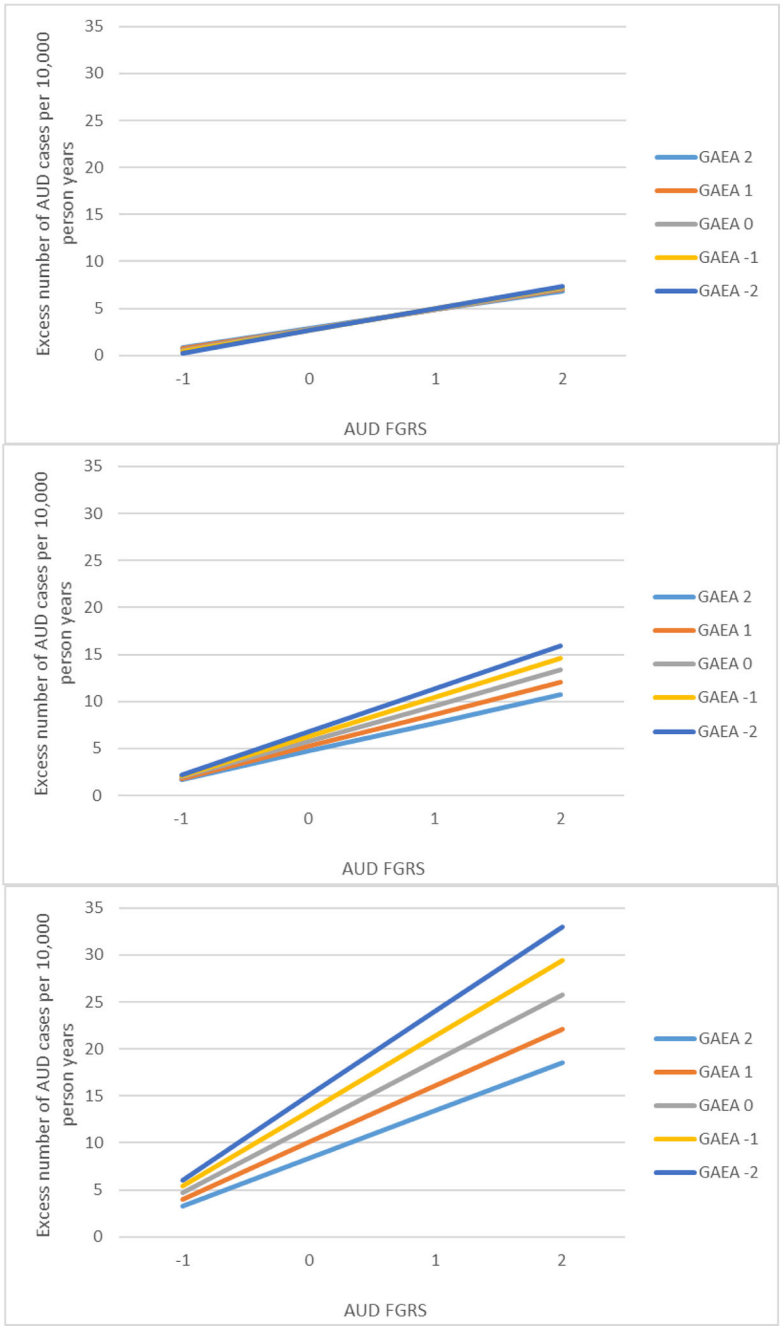


Fig. 1.

(*a*) The interaction effects in the prediction of alcohol use disorder (AUD) between the family genetic risk score for alcohol use disorder and the genetic aptitude for educational attainment. The *x*-axis is the level of the family genetic risk score for AUD in standard deviation units. The *y*-axis is the excess number of AUD cases predicted per 10 000 person

years. The colored (grey-scale) lines reflect the level of the genetic aptitude for educational attainment in standard deviation units. For example, the light blue (very light grey) line at the bottom reflects a quite high genetic aptitude for educational attainment (+2 S.D.) while the dark blue line (very dark grey) at the top of the figure reflects a quite low genetic aptitude for educational attainment (−2 S.D.). (*b*) The interaction effects in the prediction of drug use disorder (DUD) between the family genetic risk score for DUD and the genetic aptitude for educational attainment. The *x*-axis is the level of the family genetic risk score for DUD in standard deviation units. The *y*-axis is the excess number of DUD cases predicted per 10 000 person years. The colored lines reflect the level of the genetic aptitude for educational attainment in standard deviation units. For example, the light blue (very light grey) line at the bottom reflects a quite high genetic aptitude for educational attainment (+2 S.D.) while the dark blue line (very dark grey) at the top of the figure reflects a quite low genetic aptitude for educational attainment (−2 S.D.).

a



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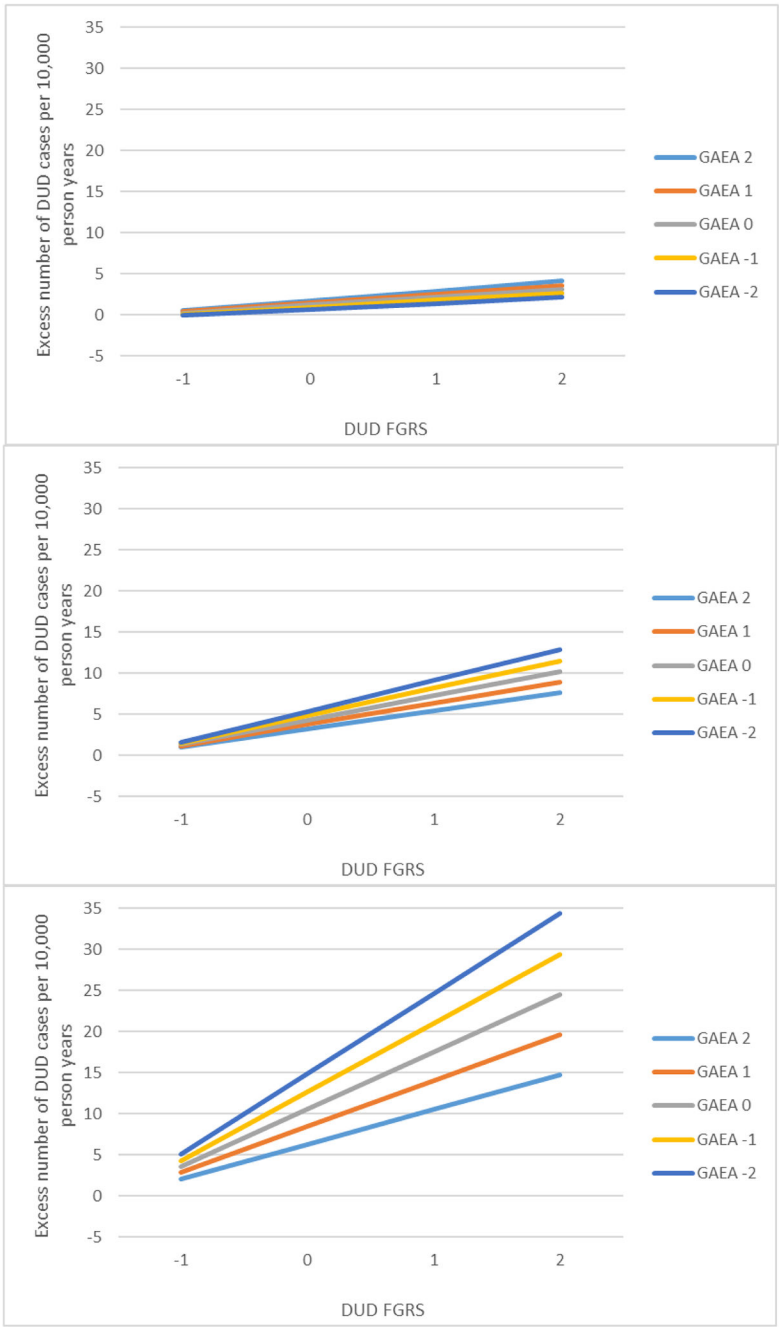

Fig. 2.

(*a*) Results of a three-way interaction analysis for the prediction of alcohol use disorder (AUD) from the family genetic risk score for AUD, the genetic aptitude for educational attainment and the actual level of achieved educational attainment. Each of the three panels is configured like that of Fig. 1a. The top panel then depicts the interaction between the family genetic risk score for AUD and the genetic aptitude for educational attainment in the prediction of AUD in individuals with high levels of achieved educational attainment (+1 S.D.). The middle figure presents the same analyses for those with an average level of

achieved educational attainment. The lowest figure presents the same analyses for those very low levels of achieved educational attainment (−2 S.D.). (*b*) Results of a three-way interaction analysis for the prediction of drug use disorder (DUD) from the family genetic risk score for DUD, the genetic aptitude for educational attainment and the actual level of achieved educational attainment. Each of the three panels is configured like that of Fig. 1b. The top panel then depicts the interaction between the family genetic risk score for DUD and the genetic aptitude for educational attainment in the prediction of DUD in individuals with high levels of achieved educational attainment (+1 S.D.). The middle figure presents the same analyses for those with an average level of achieved educational attainment. The lowest figure presents the same analyses for those very low levels of achieved educational attainment (−2 S.D.).

Table 1

Key Descriptive Statistics for Our Sample of Individuals with the Swedish General Population with Alcohol Use Disorder (AUD) and Drug Use Disorder (DUD)

	AUD	**No AUD**
N (%)	100,054 (5.4%)	1,762,381 (94.6%)
Familial Genetic Risk Score for AUD ($FGRS_{AUD}$) (Mean, SD)	0.58 (1.4)	−0.03 (1.0)
Genetic Aptitude for Educational Attainment (GAEA) (Mean, SD)	−0.34 (0.9)	0.02 (1.0)
Year of Birth (Mean, SD)	1968 (5.9)	1970 (5.9)
Males	71.8%	50.1%
Educational Attainment (EA) (Mean, SD)	−0.50 (0.9)	0.03 (1.0)
	DUD	No DUD
N (%)	62,776 (3.4%)	1,802,486 (96.6%)
Familial Genetic Risk Score for DUD ($FGRS_{DUD}$) (Mean, SD)	0.72 (1.6)	−0.02 (1.0)
Genetic Aptitude for Educational Attainment (GAEA)(Mean, SD)	−0.40 (0.9)	0.01 (1.0)
Year of Birth (Mean, SD)	1970 (6.3)	1969 (5.9)
Males	64.5%	50.8%
Educational Attainment (EA) (Mean, SD)	−0.66 (0.8)	0.02 (1.0)

Table 2

Results from Aalen's linear Hazard models (Beta Coefficients equaling excess number of cases per 10,000 person years) and 95% CIs

	Alcohol Use Disorder		Drug Use Disorder	
	Beta Coefficient	**Z-value**	**Beta Coefficient**	**Z-value**
Familial Genetic Risk Score (FGRS)	6.32 (6.21; 6.43)	64.9	4.65 (4.56, 4.74)	59.4
Genetic Aptitude for Educational Attainment (GAEA)	−2.90 (2.83; 2.97)	44.1	−2.08 (2.03; 2.13)	46.4
Year of Birth	0.11 (0.10; 0.12)	8.8	0.43 (0.42; 0.44)	24.4
Male vs Female	10.10 (9.95; 10.20)	68.9	4.08 (3.97; 4.19)	25.7
FGRS* GAEA	−1.93 (1.83; 2.03)	32.9	−1.58 (1.50; 1.66)	30.2

Table 3

Results from Three Aalen's linear Hazard models (Beta Coefficients (excess number of cases per 10,000 person years) and 95% CIs With the Latter Two Including Educational Attainment First as a Main Effect and then in Two and Three-Way Interactions*

	AUD		DUD	
	Beta Coefficient	**Z-value**	**Beta Coefficient**	**Z-value**
Model A				
FGRS	4.25 (2.16; 3.34)	70.5	3.58 (3.50; 3.66)	67.2
GAEA	−1.64 (−1.70; −1.58)	41.3	−1.67 (−1.72; −1.62)	48.5
Year of Birth	0.13 (0.12; 0.14)	15.1	0.23 (0.22; 0.23)	26.5
Male vs Female	5.81 (5.69; 5.93)	49.7	2.89 (2.79; 2.99)	30.4
FGRS * GAEA	−1.06 (−1.14; −0.98)	24.8	−1.24 (−1.32; −1.16)	28.3
Model B				
FGRS	4.08 (3.99; 4.17)	68.4	3.45 (3.37; 3.53)	66.3
GAEA	−0.41 (−0.47; −0.41)	10.8	−0.36 (−0.41; −0.31)	11.3
Year of Birth	0.13 (0.12; 0.14)	14.4	0.23 (0.22; 0.24)	25.1
Male vs Female	5.81 (5.69; 5.93)	46.0	2.87 (2.77; 2.97)	27.8
FGRS * GAEA	−1.04 (−1.12; −0.96)	24.4	−1.22 (−1.30; −1.14)	28.3
EA	−2.93 (−2.99; −2.87)	61.3	−3.08 (−3.14; −3.02)	64.0
Model C				
FGRS	3.80 (3.71; 3.89)	61.1	2.97 (2.88; 3.06)	57.3
GAEA	−0.52 (−0.59; −0.45)	12.6	−0.53 (−0.59; −0.47)	14.5
Year of Birth	0.13 (0.12; 0.14)	14.1	0.22 (0.21; 0.23)	24.8
Male vs Female	5.81 (5.69; 5.93)	46.6	2.87 (2.77; 2.97)	28.5
FGRS * GAEA	−0.39 (−0.48; −0.30)	8.2	−0.39 (−0.48; −0.30)	8.4
EA	−2.99 (−3.06; −2.92)	60.0	−3.12 (−3.18; −3.06)	63.4
FGRS* EA	−1.61 (−1.71; −1.51)	30.4	−2.01 (−2.11; −1.91)	39.6
GAEA * EA	0.57 (0.51; 0.63)	18.1	0.80 (0.74; 0.85)	28.0
FGRS* GAEA*EA	0.30 (0.22; 0.38)	7.3	0.50 (0.42; 0.58)	11.9

FGRS = Familial genetic Risk Score; GAEA = Genetic Aptitude for Educational Attainment; EA = Educational Attainment; Cases with registrations prior to age 25 are excluded (N_{AUD} = 31,851 (31.8%); N_{DUD} = 12,516 (19.9%))