



# Genetically Informative Mediation Modeling Applied to Stressors and Personality-Disorder Traits in Etiology of Alcohol Use Disorder

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## Abstract

A statistical mediation model was developed within a twin design to investigate the etiology of alcohol use disorder (AUD). Unlike conventional statistical mediation models, this biometric mediation model can detect unobserved confounding. Using a sample of 1410 pairs of Norwegian twins, we investigated specific hypotheses that DSM-IV personality-disorder (PD) traits mediate effects of childhood stressful life events (SLEs) on AUD, and that adulthood SLEs mediate effects of PDs on AUD. Models including borderline PD traits indicated unobserved confounding in phenotypic path coefficients, whereas models including antisocial and impulsive traits did not. More than half of the observed effects of childhood SLEs on adulthood AUD were mediated by adulthood antisocial and impulsive traits. Effects of PD traits on AUD 5–10 years later were direct rather than mediated by adulthood SLEs. The results and the general approach contribute to triangulation of developmental origins for complex behavioral disorders.

**Keywords** Statistical mediation model · Twin study · Causality · Stressful life events · Antisocial personality disorder · Borderline personality disorder · Substance use

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## Introduction

This paper has two primary aims: to introduce a novel statistical mediation model within a twin design and to use the model to illuminate the etiology of alcohol use disorder (AUD). The biometric mediation model offers additional value in assessing unobserved statistical confounding by combining the well-known statistical mediation model with a behavior genetic element (Baron and Kenny 1986; Neale and Cardon 1992; MacKinnon et al. 2000; Little et al. 2007; Preacher 2015). The additional value will be important, for example, when studying the life-long interplay of stressful life events (SLEs) and personality disorders (PDs) as risk factors for alcoholism, because controlled experiments are both unethical and infeasible, forcing researchers to rely on observational data and natural experiments. While we built and tested the model with this application in mind, it should be useful in a wide range of other research problems with twin data.

Behavior genetic innovations in assessing causality have traditionally followed a pattern of initial enthusiasm leading to gradual realization regarding the methods' narrow window of applicability. For example, inferences from models

of gene-by-environment interactions depend on monotonic transformations of scale, or unit, of variables, which can be problematic for behavioral measures without unambiguous physical unit (Kang and Waller 2005; Murray et al. 2016). Direction of Causation (DoC) and Mendelian randomization models often have little statistical power, depending on specific conditions for inheritance patterns of the studied variables (Heath et al. 1993; Duffy and Martin 1994; Lawlor et al. 2008), and may be difficult to interpret for complex phenotypes with time-varying or context-dependent inheritance patterns (cf. Heath et al. 1985; Krueger et al. 2008). Discordant twin designs can remove genetic variance from a hypothetical association between  $X$  and  $Y$  variables, but do not tell whether a partly genetically influenced  $X$  in fact caused  $Y$ , or vice versa (Carlin et al. 2005). Difficulty of making causal inferences is not a feature of behavior genetics, however. The history has taught us that caution and multiple vantage points are in order when attempting causal inference (Hill 1965).

Researchers using mediation models typically try to demonstrate at least two of the Hill's (1965) classic indications for causation, "temporality" (i.e., logical coherence in terms of the 'arrow of time') and "plausibility" (i.e., a mechanism to mediate the supposed causal effect). However, a 'lurking' (unobserved) confounding variable might lead to a false impression of causation in mediation models. An example would be that an unobserved gene (i.e., a confounding variable) causes two or more observed phenotypes to be associated with each other, while the environmental events that also influence these phenotypes are independent of each other. Vice versa, the phenotypic variables could be associated with each other due to some environmental event, while their genetic influences would be totally unrelated. Here, we construct a single model that supplements the logic of mediation modeling with an additional requirement of coherence in terms of inheritance patterns, with a possibility to test whether this added constraint holds in the data (i.e., test confounding). A violation would mean that different factors (genes or environments) with same observed effect on the risk phenotype imply different mechanisms and/or outcomes. In other words, preventions or interventions targeting a risk phenotype (e.g., SLEs) or its putative mediating mechanism (e.g., PDs) are not guaranteed to alter the outcome phenotype (e.g., AUD). In the parlance of Turkheimer et al. (2014), our method investigates whether "a phenotypic null hypothesis" holds for target phenotypes in a mediation model, thereby lending support to formulation of causal theory in terms of the phenotypes.

Multiple lines of research, including quasi-experiments, indicate that "exposure to stress is an important component in individual differences in risk for alcohol consumption and alcohol use disorders" (Keyes et al. 2011). SLEs are associated with alcohol craving and AUD, and a history of

childhood maltreatment further strengthens the association (Boden et al. 2014; Kim et al. 2014; Just-Østergaard et al. 2018). However, it is unclear how SLEs exert an effect on AUD. For instance, the role of personality disorders (PDs) in the relationship between SLEs and AUD remain unclear despite high rate of comorbidity between PDs and AUD (Flensburg-Madsen et al. 2009; Kim et al. 2014). While SLEs are typically considered as environmental exposures, genetic factors are associated with exposure to SLEs (Kendler and Baker 2007)—possibly because common genetic factors underlie personality traits, which affect what environments an individual seeks and how others react to him or her (McAdams et al. 2013). All the 10 PDs are associated with AUD in large datasets (Trull et al. 2010), and both PDs and AUD are influenced by genetic factors (Kendler et al. 2008; Ystrom et al. 2014). Therefore, possible confounding variables may make ordinary mediation models infeasible. At the same time, the questions whether effects of childhood SLEs on AUD are mediated by PDs, or effects of PDs on AUD by adulthood SLEs, are of substantial etiologic importance. Here we address these questions using a biometric modeling approach that provides a degree of control over unobserved confounding by being able to test for it.

Regarding specific personality pathologies, childhood SLEs have been suggested to play a role in development of antisocial and borderline PD traits (Jaffee et al. 2004; Afifi et al. 2011; Hyde et al. 2016; Baryshnikov et al. 2017), although a biometric study reported that the association with borderline PD may be subject to unmeasured genetic confounding (Bornovalova et al. 2013). These two DSM-IV PDs have been found to be associated with AUD even after adjusting for the other eight PDs (Long et al. 2017). In addition, two of their criteria, childhood conduct disorder (antisocial PD criterion #8) and self-harming impulsivity (borderline PD criterion #4), have been found to be associated with AUD even after adjusting for all the 80 DSM-IV PD criteria (Rosenström et al. 2018). Removing the AUD-oriented borderline PD criterion #4 from the analysis, antisocial PD criterion #1 (violations of social norms for lawful behavior) emerged from the remaining 79 criteria (Rosenström et al. 2018). These criteria are likely to be associated with intermediate phenotypes related to impulsivity that follow from childhood SLEs (Castellanos-Ryan et al. 2011; White et al. 2014; Barker et al. 2015; Gondré-Lewis et al. 2016; Mackey et al. 2017). On the other hand, these PD traits could also invoke adulthood SLEs, which then increase AUD risk (Boden et al. 2014; Kim et al. 2014).

In summary, the specific aims of the current study are (1) to introduce a biometric mediation model and (2) to use it to estimate the directed mediational paths from childhood SLEs to AUD through the above-discussed PD traits, while controlling for inheritance patterns indicative of confounding variables. We also (3) estimate the extent to which

mediation through adulthood SLEs explains the prospective associations between the key PD traits and AUD. Our approach is motivated by the notion that claims of causation are strengthened by (i) plausible (mediating) mechanism and (ii) evidence towards lack of lurking confounders, as well as discussion on other convergent research (e.g., animal experiments).

## Methods

### Participants

We analyze a population-based sample of Norwegian twins recruited from the Norwegian Institute of Health Twin Panel (Nilsen et al. 2013). Written informed consent has been obtained from all participants after a complete description of the study. Zygosity was determined by a combination of questionnaire items and genotyping, resulting in a less than 1% miss-classification rate, which is unlikely to substantially bias results (Neale 2003). The sample has two waves of assessment pertinent to this study, for which we received approval from The Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics.

All twins born between 1967 and 1979 were invited to participate in the original study and 63% responded. Complete twin pairs who responded were invited to psychiatric interviews between the years 1999 and 2004, and wave 1 PDs were assessed at interview in 2801 twins [43.5% of those who were eligible; 1390 complete twin pairs and 21 single twins, which broke down to 225 full or partial monozygotic (MZ) male pairs, 453 MZ female pairs, 297 dizygotic (DZ) male pairs, and 435 DZ female pairs]. Participants mean age was 28.2 years and age range 19–36. Altogether 2284 twins (987 complete pairs and 310 single twins) were re-interviewed with telephone approximately 10 years later, between 2010 and 2011 (wave 2; response rate 83%). A total of 2299 twins (response rate 83%) also filled in a mailed questionnaire on SLEs.

### Measurements

Personality disorders within past 5 years were assessed using a Norwegian version of the Structured Interview for DSM-IV Personality (Pfohl et al. 1995), a comprehensive semi-structured interview of all DSM-IV Axis II diagnoses, rating the specific DSM-IV criteria according to following coding: 0 = not present or limited to rare isolated examples; 1 = subthreshold (some evidence of the trait, but not sufficiently pervasive for the criterion to be considered present); 2 = present (criterion clearly present for most of the time during last 5 years); 3 = strongly present

(associated with subjective distress or some impairment in social or occupational functioning or intimate relationships). At wave 1, a face-to-face interview was conducted for all but 231 individuals interviewed over telephone for practical reasons. All wave 2 interviews were conducted by telephone. Interviewers were mainly senior clinical psychology graduate students and experienced psychiatric nurses. Each twin in a pair was interviewed by a different interviewer. Two interviewers re-scored 95 recorded interviews at wave 2 to assess inter-rater reliability: at sub-threshold level, their respective criterion counts correlated (polychoric  $r$ ) at 0.838 for antisocial PD and 0.832 for borderline PD. Tetrachoric inter-rater correlations of the specific criteria of interest here were 0.838, 0.780, and 0.643 for childhood conduct disorder (necessary criterion for antisocial PD), self-harming impulsive behaviors (borderline PD criterion #4), and failure to conform to social norms with respect to lawful behavior (antisocial PD criterion #1), respectively.

We combined diagnoses for alcohol dependence and/or alcohol abuse and refer to the ensuing variable as “alcohol use disorder” (AUD). The two diagnoses have been merged in DSM-5 as well (American Psychiatric Association 2013). At both waves, AUD was assessed using the computerized Norwegian version of World Health Organization’s Composite International Diagnostic Interview (Wittchen and Pfister 1997). The AUD diagnosis refers to 5-year recency of AUD; i.e., fulfilling the criteria at the time of interview or at any time during the 5 years preceding the interview. The 5-year recency was chosen for consistency with the diagnostic period for the PDs and provides a reasonable number of both AUD cases and SLEs that fall between first interview and the second 5-year diagnostic period. Kappa values of 0.78 have generally been reported for AUD, providing an estimate of reliability (Wittchen et al. 1998).

Table 1 lists all the SLEs assessed in the wave 2 questionnaire. For each SLE, participants were asked to report the age at the time it occurred, allowing us to time the events with a ~1-year precision. We estimated reliability of the SLE count variable to be 0.755 based on the agreement between twins for events that should be shared by both the twins (see supplementary material for details). Logical temporal ordering of events was retained when studying the potential mediation pathways (Preacher 2015). Childhood SLEs consisted of a count of SLEs before age 16 (“Childhood” column in Table 1). SLEs occurring after wave 1 PDs but before possible wave 2 AUD consisted of a count of SLEs after the first interview but no closer than 5 years to the second (“Intermediate” in Table 1). In addition to the SLE data summarized in the Table 1, our analysis was based on PD and AUD data summarized in previous studies (Reichborn-Kjennerud et al. 2013, 2015; Long et al. 2017; Rosenström et al. 2017, 2018; Torvik et al. 2017).

**Table 1** Frequencies of stressful life events

No	Short description	Childhood <sup>a</sup>	Intermediate <sup>b</sup>	Any/total <sup>c</sup>	Missing <sup>d</sup>
1	Life-threatening illness	40	23	115	525
2	Serious/life-threatening accident	35	16	143	517
3	Direct combat experience in war	0	2	29	508
4	Witnessed a bad injury or kill	31	31	203	538
5	Threatened, captive, or kidnapped	20	11	146	517
6	Fire, flood, or natural disaster	30	18	127	515
7	Raped	27	4	86	513
8	Sexually abused or molested (non-rape)	113	1	166	519
9	Otherwise physically attacked/assaulted	70	27	283	539
10	Otherwise physically abused as a child	66	0	68	518
11	Otherwise mistreated as a child	55	0	56	523
12	Parental alcohol or mental problem as a child	252	1	270	638
13	Parents divorced or moved apart when child	317	2	418	540
14	Own divorce or broken engagement	4	185	633	585
15	Major financial difficulties lasting over time	6	32	136	542
16	Unemployed for more than 6 months	7	46	191	559
17	Major lasting conflict with a close person	17	54	254	530
18	Anything else bad to mention in this section	57	76	350	630

<sup>a</sup>Before age 16

<sup>b</sup>After 1st interview and 5 or more years before the 2nd interview

<sup>c</sup>Any time

<sup>d</sup>A missing observation that could have been a stressful life event or not, or was an untimed event. Most missing observations are not due to item non-response but due to drop out from wave 1 to wave 2. The SLE questionnaire was filled in in the latter wave

## Statistical modeling

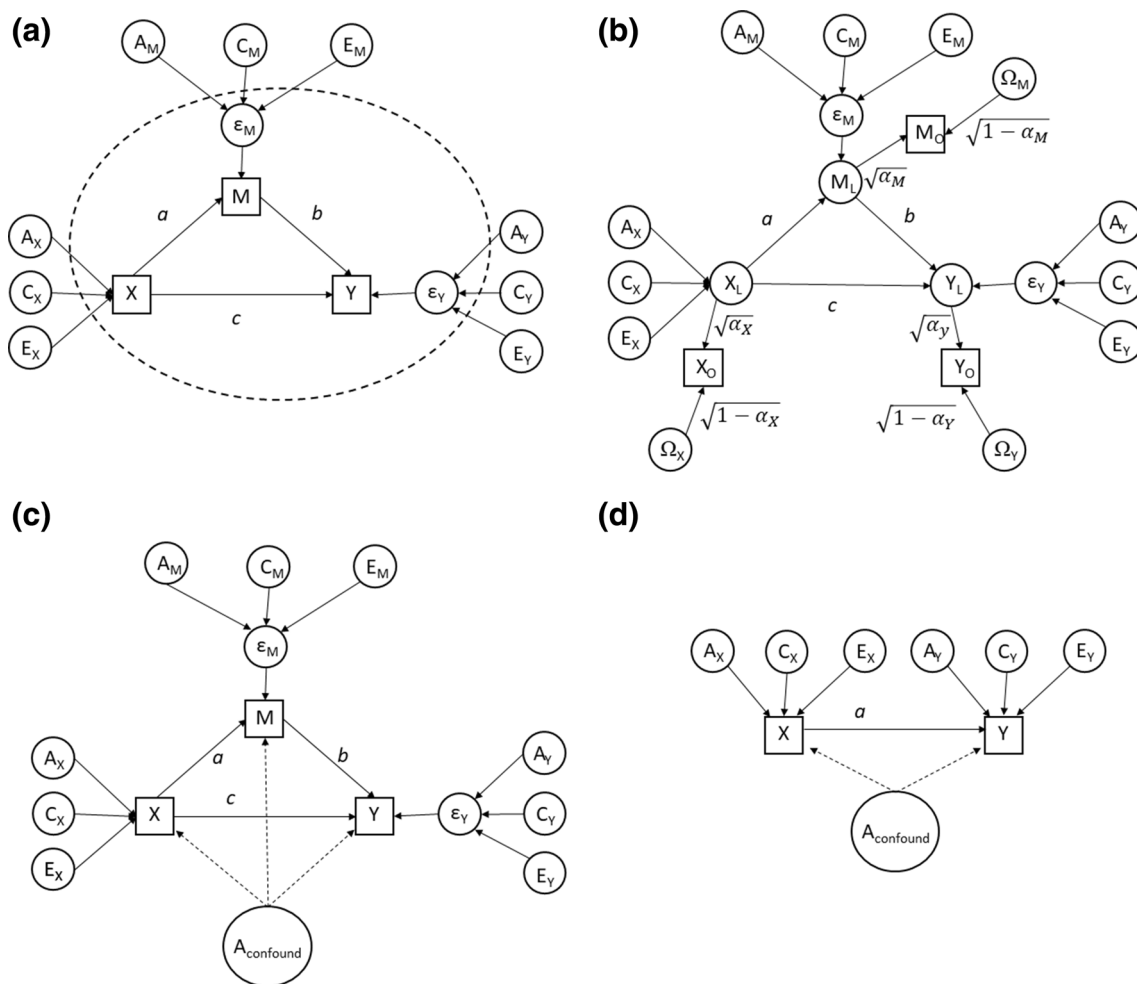
Because MZ twins share 100% of their segregating genes and DZ twins on average 50%, observing their respective phenotypic correlations provides a rationale for partitioning the covariance structure of the phenotypic variables into latent Additive genetic effects (A), Common or shared environmental exposures that make twins similar (C), and non-shared Environmental effects (E), which encompass all influences contributing to making twins different (Neale and Cardon 1992). Thus, a twin design makes the latent biometric parts of the observable variables statistically accessible.

Statistical mediation is typically assessed using a model whose path diagram is depicted within the dashed-line ellipse in Fig. 1a. However, such mediation models do not control for possible unobserved confounding, implicitly assuming that all three biometric sources of variance conform to the same phenotypic mediation and/or direct pathways. If one has only phenotypic data, the mediation model fits perfectly with any conceivable covariance matrix (i.e., is saturated) and questions of unobserved genetic or environmental confounding cannot be evaluated. A twin design, however, makes it possible to examine the structure outside the dashed-line ellipse in Fig. 1a, and leads to an over-identified model that can be tested. We refer to this

path structure as the *biometric mediation model*. This is a clear improvement over the classic mediation model in the sense that the mediation effect is no longer computed “in the same manner regardless of whether the effect is causal or correlational” (MacKinnon et al. 2000), and important to consider in context of comorbidity between AUD and PDs (Flensburg-Madsen et al. 2009).

The biometric mediation model is compared to a model where all sources of variance, A, C, and E, have freely estimated covariance structures that can be independent from each other. For example, a Cholesky model of behavior genetics will do the job (Neale and Cardon 1992; Loehlin 1996). If the Cholesky model fits better than the biometric mediation model, then the idea that the statistical mediation relation reflects an actual causal process is seriously confounded when examining biometric data. Cholesky model will fit better than the mediation model, for example, when there is a ‘gene’ that directly affects all the phenotypes (cf. Fig. 1c), but also for many other cases, including confounders in any of the A, C, or E components, as well as any combinations that cannot be fitted with the biometric mediation model.

Low reliability (low  $\alpha$ ) can bias mediation parameters and contribute to model misfit, but the problem can be addressed using some form of error-in-variables (EIV) modeling



**Fig. 1** Alternative biometric models. Boxes represent observed variables and circles latent variables. Symbol “A” stands for additive genetic influences and “C” for common/non-shared and “E” for shared environmental influences. Subscripts either associate a latent variable with an observed variable (X, M, or Y), or denote a latent variable with “L” and observed variable with “O”. Arrows represent path coefficients, or equivalently, ‘regression’ effects of one variable

on another. Panels show different models: **a** Biometric mediation model. **b** Biometric mediation model for variables observed with reliability  $\alpha_T$ , where T is the variable in question. **c** Biometric mediation model subject to genetic (“A-type”) confounding. We similarly investigated C- and E-type confounding. **d** Direction of Causation (DoC) model under possible genetic confounding

(Fig. 1b, e.g., Carroll et al. 2006). EIV models acknowledge and attempt to remove (or “disattenuate”) effects of measurement error based on some estimates of reliability ( $\alpha$ 's in Fig. 1d; see “Measurements” for our values), thereby returning the model to the case of Fig. 1a but without bias from measurement errors (e.g. Carroll et al. 2006). We refer to this model as an *EIV-mediation model* and provide technical details in the supplementary online file.

Finally, the Direction of Causation (DoC; Fig. 1d) model provides a useful point of comparison for the present methodology (Heath et al. 1993; Duffy and Martin 1994). The DoC models use information on the biometric A, C, and E sources of variance to distinguish a “directional dependence” (causality) between variables from observational data (Wiedermann and von Eye 2016). In the “Results”, we

examine how effectively the established DoC models can detect a confounder (dashed-line effects in Fig. 1d) in comparison to the biometric mediation model (cf. Fig. 1c). We use a classic method for statistical power analysis: derive the theoretical covariance matrices for MZ and DZ twins, fit the model and the alternative, and use chi-squared statistic from their comparison as the non-centrality parameter of a chi-squared test-statistic distribution in the power analysis (Neale and Cardon 1992).

We use Akaike’s information criterion (AIC) to compare several models in real data (Vrieze 2012; Burnham and Anderson 2004; Wagenmakers and Farrell 2004). Lower values of AIC indicate better model parsimony, that is, fit accounting for the number of freely estimated parameters (or model complexity, or risk for overfitting). For example,

a difference of 4 or more is “considerable”, whereas 2 or less implies only a small difference between the models (Burnham and Anderson 2004). In addition to such rules of thumb, we provide the probability of the EIV-mediation model being the ‘Kullback–Leibler best’ model when comparing to the Cholesky model (Burnham and Anderson 2004). Because AIC penalizes less from the extra parameters of the Cholesky model compared to, e.g. Bayesian information criterion (BIC), it is relatively conservative in suggesting causal mediation when used to compare the Cholesky and the biometric mediation model against each other. In terms of model complexity, BIC approaches its ‘target’ model from below as sample size grows, meaning it would eschew the generously parameterized Cholesky model in finite samples (Vrieze 2012; Burnham and Anderson 2004; Wagenmakers and Farrel 2004). In cases where the biometric mediation model, or the EIV-mediation model, was unconfounded (i.e., supported over the Cholesky model), quantities familiar from ordinary statistical mediation studies were computed. Namely, the mediated (i.e., indirect) effect is estimated by the product of  $a$  and  $b$  path coefficients ( $ab$ ), the direct effect by  $c$ , and the total effect by  $ab + c$  (cf. Fig. 1a); the percentage of the total effect that gets mediated is  $ab / (ab + c) \times 100\%$ . Note that we do not compare the non-EIV biometric mediation model to the EIV-mediation model in terms of AIC because these models implement the same idea and have the same complexity. Instead, our use of the two models constitutes a sensitivity analysis for measurement error when comparing these models to the Cholesky model.

We modeled the ordinal-valued observed variables using a liability-threshold model that assumes an underlying continuous latent variable and allows different category endorsement rates for men and women (Neale and Cardon 1992; Neale et al. 2016; Rosenström et al. 2017). Past studies have demonstrated the need for sex-specific thresholds in context of the PDs studied here (Kendler et al. 2012; Reichborn-Kjennerud et al. 2013; Rosenström et al. 2017). To avoid frequent empty cell conditions, counts of SLEs of three or more were collapsed. Similarly counts of five or more borderline PD criteria and four or more antisocial PD criteria were collapsed. When studying individual criteria, endorsements at levels “present” and “severe” were collapsed. Throughout, we used full information maximum likelihood estimation (Enders and Bandalos 2001), and report likelihood-based 95% confidence intervals (Neale and Miller 1997).

We tested the mediation models by way of simulations carried out in Open Mx software version 2.6.9 with “NPSOL” optimizer, running in R version 3.3.1 for Windows 10 (Neale et al. 2016). More details on these results and on the applied models can be found from the supplementary online file. We analyzed our Norwegian participant data in Open Mx version 2.7.9, running in R version 3.1.2. RC on Windows 10 server for sensitive data analysis.

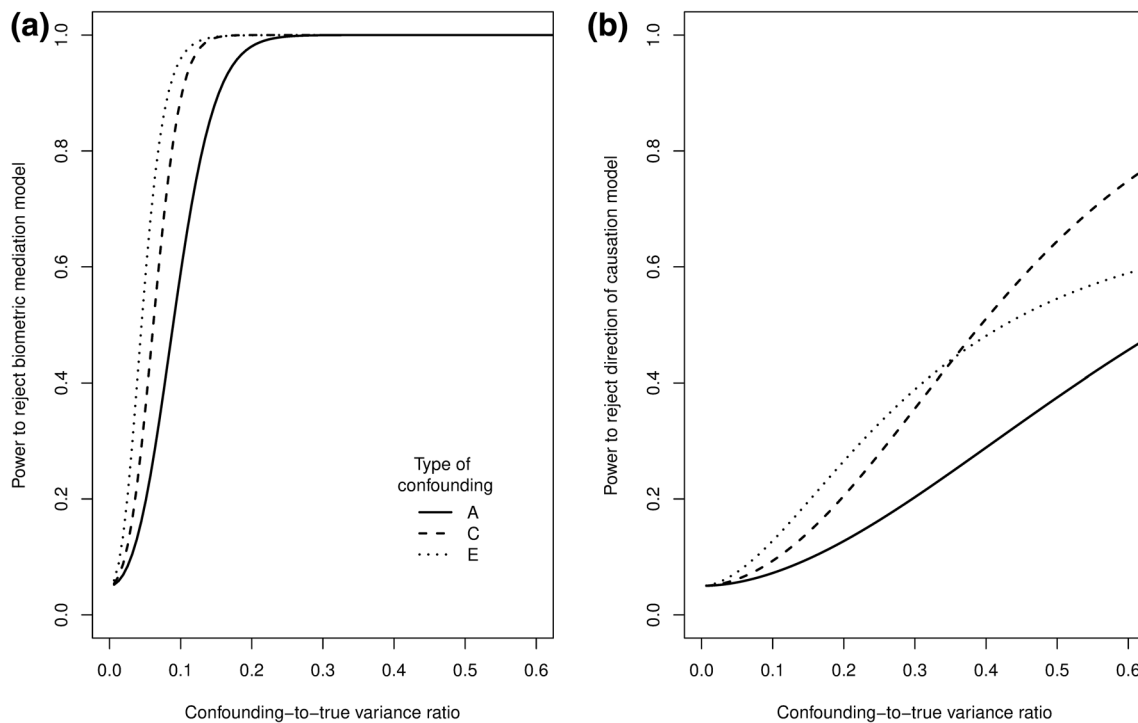
## Results

### Theoretical results on biometric mediation model

Our simulation analyses (see supplementary material) indicated that estimating the full biometric mediation model did not inflict mentionable efficacy costs in the model parameters shared with the classic, genetically uninformative, mediation model. This allowed us to consider it an improvement of mediation analysis rather than a trade-off in aims. We then sought for quantitative understanding on the novelty it provides over ordinary mediation analysis—power to detect confounding. Analysis of statistical power often becomes cumbersome for behavior genetic models because so many parameter constraints could be tested for. However, DoC models are an older method that allows us to highlight some of the relative benefits of biometric mediation models. The DoC models use twin design to distinguish genuine phenotypic dependence from confounded correlations, but the biometric mediation model further proposes a mechanism of action. The proposed mechanism (i.e., the mediator) is a third variable that can offer significant gains in terms of statistical power (Schmitz et al. 1998).

In DoC modeling, one might try to establish that the fit of a DoC model does not statistically significantly differ from a (Cholesky) model with arbitrary genetic and shared and non-shared environmental correlations (i.e., that we cannot reject it as a plausible explanation for the data in question). Of particular interest there is detection of a source of confounding that does not fit with the proposed directionality (i.e., detection of dashed-line effects in Fig. 1d). Similarly, in the biometric mediation modeling we would wish to detect a confounder of an unspecified nature (e.g., that in Fig. 1c) by comparing the mediation model to a more general (i.e., the Cholesky) model. Figure 2 shows an analysis of statistical power for these respective cases when all the regression coefficients were set to value 0.8 and the biometric sources of variance to variance 1/3 (see supplementary material for derivations). The horizontal axis shows the amount of introduced confounding as the average ratio of variance per variable and the vertical axis shows the associated statistical power to detect it. The consideration for mechanism in the biometric mediation model pays off in terms of higher power to detect violations of hypothesized causation in comparison to DoC models (Fig. 2).

The intuition behind this analytic result is two-fold. First, pairwise direction of causation is not estimable from cross-sectional correlations. There are 0 degrees of freedom. The (different) MZ and DZ twin correlations provide a user of the DoC model with 2 degrees of freedom



**Fig. 2** Statistical power to detect confounding. **a** Power when comparing biometric mediation model to a Cholesky model with unconstrained additive genetic (A) and non-shared (C) and shared (E) environmental covariance structures, plotted as a function of the degree of A-, C-, and E-type confounding. The confounder always had a uniform influence on all variables, as illustrated in Fig. 1c. **b** Power in a

similar analysis for the direction of causation model (cf. Fig. 1d). The analysis is based on 678 monozygotic and 732 dizygotic twins and continuous-variate (non-EIV) versions of the respective models, with all phenotypic regression coefficients at 0.8 and all unconfounded A, C, and E variances at 1/3

that might differentiate directionality from confounding, thereby providing statistical power to where there was none (Heath et al. 1993). The biometric model is a more restrictive hypothesis and provides 6 degrees of freedom in a direct analogy, and thus more potential power. Second, and at the same time, the confounder (a deviation from biometric mediation) is ‘measured’ with three variables instead of just two, and very efficiently by definition (i.e., the confounding-variance part is perfectly correlated across the ‘indicators’). For example, Schmitz et al. (1998) reported 2.7-fold power (0.76 vs. 0.28) to detect presence of 30% heritable genetic sources among four variables when their correlation increased from 0 to 0.8. The combination of these two effects makes the biometric mediation model a potentially very powerful tool to investigate confounding. Note, however, that these desirable power characteristics are not present to a comparable extent in all conceivable applications; for example, there is no biometric information in the exposure of randomized experiments because it is a purely environmental variable, by definition (i.e., forced by the experimenter; cf. Fritz et al. 2016). In what follows, we use a model comparison criterion instead of null-hypothesis testing as it is a more suitable tool (see

Methods), but the gains in power are nevertheless present implicitly.

## Real-data results

Results from the model comparisons are provided in Table 2. The EIV version of the biometric mediation model always fit these data better than the non-EIV model, indicating that explicitly modeling measurement error generally improved the biometric mediation model. However, modeling of measurement errors did not affect the relative order of biometric mediation versus Cholesky models in AIC, indicating robustness of qualitative inferences against the measurement errors (Table 2). Because both the mediation models fit data better than the Cholesky model in the exact same instances, and the EIV-mediation model invariably fit better than the non-EIV mediation model, we can improve the flow of essential ideas in what follows by referring to the EIV-mediation model as the biometric mediation model unless separately mentioned, while always discussing about the model-derived error-free unbiased mediation parameters rather than the biased parameters of the non-EIV model. We

**Table 2** Model fitting results for all the studied models

Temporality	PD variable	Biometric mediation model AIC	EIV mediation model AIC	Cholesky model AIC	$P_{K-L \text{ best}}$
SLEs → PDs → AUD	Antisocial PD	–5592.02	– <b>5592.45</b>	–5587.58	0.919
	Borderline PD	–2818.79	–2820.2	– <b>2821.82</b>	0.308
	Conduct disorder	–7427.99	– <b>7431.82</b>	–7426.05	0.947
	Impulsivity	–7015.5	– <b>7021.92</b>	–7013.14	0.988
	Failure to conform	–8441.89	– <b>8446.2</b>	–8437.01	0.990
PDs → SLEs → AUD	Antisocial PD	–6610.9	– <b>6613.25</b>	–6610.49	0.799
	Borderline PD	–3820.46	–3824.8	– <b>3829.04</b>	0.107
	Conduct disorder	–8444.46	– <b>8445.12</b>	–8441.5	0.859
	Impulsivity	–8055.36	– <b>8059.96</b>	–8053.07	0.969
	Failure to conform	–9478.97	– <b>9481.16</b>	–9472.86	0.984

Temporality refers to relative timing of the recorded stressful life events (SLEs), personality disorder (PD) traits, and alcohol use disorder (AUD), and “AIC” refers to Akaike’s Information Criterion (lower value indicates better fit; best-fitting model per row are highlighted in bold). “EIV” refers to an “error-in-variables” version of the biometric mediation model that removes the effects of pre-estimated amount of measurement error.  $P_{K-L \text{ best}}$  is the probability that the EIV-mediation model is the (Kullback–Leibler) best model when comparing to the Cholesky. Regarding “PD variables”, antisocial and borderline PD refer to DSM-IV criterion counts as the PD trait, whereas “impulsivity” refers to underlying liability to self-harming impulsive behaviors as defined in criterion #4 of borderline PD, “failure to conform” refers to liability to violate social norms with respect to lawful behavior as defined in criterion #1 of antisocial PD, and “conduct disorder” refers to childhood conduct disorder, a prerequisite of antisocial PD diagnosis

first discuss the results for childhood SLEs as an exposure and then for SLEs as an adulthood mediating variable.

### Childhood SLEs as an antecedent for personality-mediated alcoholism

The five first rows of Table 2 present model-comparison results between the biometric mediation model, the EIV-mediation model, and the Cholesky model for the five adulthood PD-trait mediators of childhood SLE-based AUD risk. The biometric mediation model using antisocial PD data fit better than the Cholesky model according to AIC, whereas the model including borderline PD fitted less well (Table 2). The biometric mediation model was the model of choice for all the criterion level PD traits (Table 2). We present the biometric mediation models here. For comprehensiveness, the supplementary Table S1 gives the genetic and environmental correlations among SLEs, borderline PD, and AUD, even though we rejected the mediation model due to confounding.

Figure 3 displays parameter estimates of the biometric mediation models for childhood SLEs, showing that shared environmental (C) influences in AUD derive both from childhood trauma and from residual sources. Most of the additive genetic (A) influences in AUD derive from the PD related genetic liabilities, whereas the non-shared environmental (E) influences in AUD derive from both PD-related variance and residual effects of AUD (notice that effects of measurement error have been removed from these path diagrams by EIV modeling). Given that no confounding was detected, we present also the quantitative phenotypic mediation estimates derived from the biometric models:

direct effects from childhood SLEs to AUD were statistically non-significant, whereas the indirect (i.e., PD-mediation) effects were always statistically significant (Table 3). Overall, roughly 6% of the latent AUD liability was explained by childhood SLE count, and more than half of the effect was mediated by a PD trait.

### Adulthood SLEs as a mediating factor of personality-related AUD liability

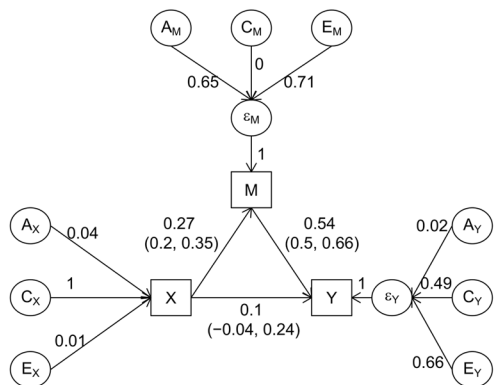
As noted in the above discussed models, borderline PD was again the only PD variable in our analysis that resulted in an indication of confounding and therefore did not support biometric mediation modeling (Table 2). The remaining PD traits had a statistically significant direct effect on AUD, but no indirect effect via the adulthood SLEs (Table 3 and Supplementary Fig. S5). The biometric decomposition was in line with Fig. 3 where relevant, but adulthood SLEs differed from childhood SLEs by having no C component (Supplementary Fig. S5).

## Discussion

We combined a statistical mediation model with a genetically informative twin design to study more in-depth the etiology of AUD with respect to its PD- and SLE-related risk factors, concentrating on the previously established behavioral risk traits for AUD (Long et al. 2017; Rosenström et al. 2018). We called the ensuing model ‘the biometric mediation model’ and compared its power properties to those of

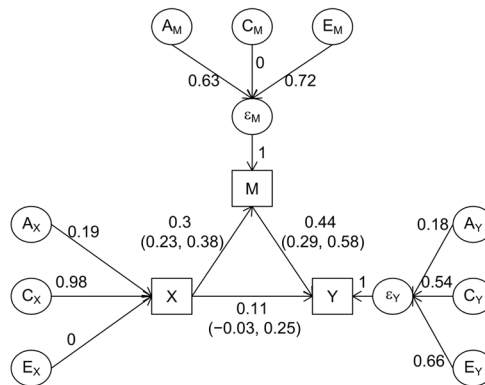


(a) X = SLEs, M = Antisocial PD, Y = AUD



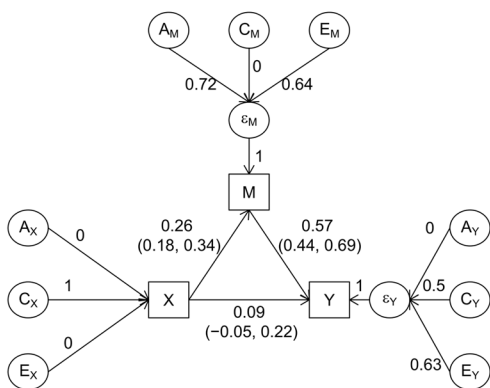
Proportion mediated: 59.6%

(b) X = SLEs, M = Conduct Disorder, Y = AUD



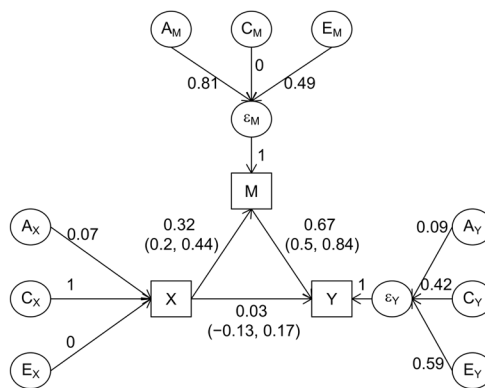
Proportion mediated: 53.9%

(c) X = SLEs, M = Self-harming impulsive behaviors, Y = AUD



Proportion mediated: 63.3%

(d) X = SLEs, M = Failure to conform, Y = AUD



Proportion mediated: 86.3%

**Fig. 3** The “unconfounded” biometric mediation models for childhood stressful life events (SLEs), adulthood personality disorder (PD) traits, and alcohol use disorder (AUD). “Unconfounded” refers to the

DoC models. These models have different applications in that the biometric mediation model is intended for study of mediating mechanisms, providing further support on top of other principles of causal inference and theory building (see e.g. Hill 1965; Wiedermann and Von Eye 2016; Lawlor et al. 2017), whereas DoC models are frequently used to distinguish between competing directions of causation purely on statistical grounds (see e.g. Nesvåg et al. 2017 for a typical application). Both models are concerned with possibility of confounding, however, and we showed by statistical power analysis that willingness to consider mediating mechanisms can considerably increase chances of detecting confounded causal hypotheses. In other words, the biometric mediation model can inform about unobserved confounding where ordinary mediation models cannot, and it is more powerful

models not being rejected in favor of more general hypotheses comprised by the Cholesky model of behavior genetics. **a–d** Show parameter estimates for models using different PD traits

at doing so than bivariate DoC models in typical cases with correlated sources of variance (see Schmitz et al. 1998 for a general discussion on power).

We found out that the phenotypes of antisocial PD, childhood conduct disorder, self-harming impulsive behaviors, and failure to conform to social norms of lawful behavior resulted in unconfounded biometric mediation models of SLEs, PDs, and AUD, whereas confounding was indicated for borderline PD. Childhood SLEs explained roughly 6% of adulthood AUD liability (total effect squared  $\times$  100%), more than half of which was mediated by an adulthood PD trait. The effects of the adulthood PD traits on AUD were direct rather than mediated by adulthood SLEs, explaining ~22–48% of AUD liability. Twin pairs’ shared environmental influences on AUD and PDs mainly derived from the

**Table 3** Phenotypic mediation estimates based on selected biometric EIV mediation models

Temporality	PD variable	Total effect	Direct effect	Indirect effect	Proportion mediated
SLEs → PDs → AUD	Antisocial PD	0.247 (0.111, 0.375)	0.100 (−0.044, 0.236)	0.147 (0.099, 0.207)	0.596 (0.335, 1.387)
	Conduct disorder	0.247 (0.115, 0.374)	0.114 (−0.03, 0.255)	0.133 (0.082, 0.196)	0.539 (0.277, 1.256)
	Impulsivity	0.235 (0.105, 0.362)	0.086 (−0.053, 0.223)	0.149 (0.095, 0.215)	0.633 (0.341, NA)
	Failure to conform	0.249 (0.116, 0.377)	0.034 (−0.125, 0.166)	0.215 (0.124, 0.273)	0.863 (0.447, NA)
PDs → SLEs → AUD	Antisocial PD	0.569 (0.452, 0.676)	0.555 (0.44, 0.667)	0.014 (NA, 0.045)	0.025 (−0.024, 0.082)
	Conduct disorder	0.471 (0.335, 0.596)	0.454 (0.316, 0.582)	0.017 (−0.003, 0.047)	0.036 (0.017, 0.105)
	Impulsivity	0.597 (0.469, 0.713)	0.583 (0.448, 0.703)	0.014 (−0.024, 0.05)	0.023 (0.014, 0.089)
	Failure to conform	0.691 (0.53, 0.834)	0.677 (0.513, 0.822)	0.015 (−0.009, 0.043)	0.021 (−0.013, 0.065)

Temporality refers to relative timing of the recorded stressful life events (SLEs), personality disorder (PD) traits, and alcohol use disorder (AUD), and “EIV” refers to the “error-in-variables” version of the mediation model. Parentheses give 95% likelihood-based confidence intervals (Neale and Miller 1997); “NA” (not available) is substituted in place of the three interval boundaries that could not be reliably estimated by Open Mx software. Each row of the table corresponds to a different biometric mediation model. Antisocial PD refers to DSM-IV criterion count as the PD trait, whereas “impulsivity” refers to underlying liability to self-harming impulsive behaviors as defined in criterion #4 of borderline PD, “failure to conform” refers to liability to violate social norms with respect to lawful behavior as defined in criterion #1 of antisocial PD, and “conduct disorder” refers to childhood conduct disorder, a prerequisite of antisocial PD diagnosis

childhood SLEs, whereas additive genetic and non-shared environmental influences in AUD partly derived from those of the PDs and from those unique to AUD, but not from SLEs. Measurement error was removed via EIV modeling prior to interpretation of the biometric variance sources.

Our model-selection findings make sense in light of previous biometric findings in the same data, according to which antisocial PD criteria align with a single common factor plus residual sources whereas the borderline PD involves a more complex multidimensional structure (Reichborn-Kjennerud et al. 2013; Rosenström et al. 2017). In general, the more complex the structure the greater the likelihood of confounding. Also biometric studies in other datasets have reported genetic confounding in association between childhood SLEs and a composite index of borderline PD (Bornovalova et al. 2013). In contrast, previous studies demonstrate both genetic and environmental transmission of the effects of childhood SLEs on adult antisocial traits, and that antisocial traits further expose individuals to AUD (Jaffee et al. 2004; Kim et al. 2014; Hyde et al. 2016; Long et al. 2017; Rosenström et al. 2018). And, the impulsivity sub-component of borderline PD appears to have stronger links with both childhood SLEs and AUD risk (Castellanos-Ryan et al. 2011; Gondré-Lewis et al. 2016; Rosenström et al. 2018). Also evidence on biological mechanisms exist, as brain regions and functions underlying impulsive behaviors are affected by childhood stress in studies of animals and humans, and they control excessive drinking behavior in animal studies (Gondré-Lewis et al. 2016; Mackey et al. 2017). Thus, the phenotypes we found here to be unconfounded mediation pathways also appear to reflect true phenotypic effects in other research, and vice versa.

By being able to test whether latent biometric sources of variance are unconfounded, the biometric mediation method

could supplement the existing set of models for causal inference, for example, in a process of triangulation in etiologic inference (Lawlor et al. 2017). A “triangulation” process acknowledges that observational methods of causal inference all tend to rely on untestable assumptions, but often on different sets of assumptions. Thus, each additional method with non-overlapping assumptions rules out some of the possible errors of inference. Regarding other well-known biometric methods for causal inference, the biometric mediation model is similar to Mendelian randomization in assuming that effects of genes are passed on from one phenotype to another, but requires no explicit gene or instrument variable (Didelez and Sheehan 2007; Lawlor et al. 2008). It differs from discordant twin analyses that treat all genetic variance as confounding variance by assumption (Carlin et al. 2005; McGue et al. 2010). Yet, it can detect genetic confounding when the genetic and environmental covariances are inconsistent with phenotypic mediation hypothesis. The biometric mediation model is strictly unbiased only when corrected for measurement error (see online supplement), but in this study, the bias from failure to correct for measurement error would have been small enough not to alter conclusions regarding confounding (Table 2). More generally, the direction of bias in the parameter estimates is known and its magnitude moderate (Supplementary Fig. S4). In this sense, the biometric mediation model appears robust. Of course, it cannot definitively prove causation, but only improves over classic mediation model by being able to falsify causal hypotheses and detect confounding. All statistical models aimed to address causation should be tested from multiple vantage points (Hill 1965; Wiedermann and von Eye 2016; Lawlor et al. 2017).

Biometric mediating modeling adds to techniques of causal analysis and helps in cases where confounding

variables are ‘visible’ in behavior genetic analysis. For example, the model could detect possible confounding effects of peer-group delinquency, which could feasibly influence the environmental exposure to SLEs, PDs, and AUD, *without* affecting their genetic component. Or it could detect a direct genetic influence on all the observed variables. However, it could not detect a ‘systemic’ confounder that affects all the biometric components simultaneously, at the same phenotypic level with the variables of interest. When such “systemic” confounders are observed, researchers could add them as covariates to the biometric mediation model in a direct analogy to non-biometric mediation models or try developing an inverse probability weighted version of the model (Coffman and Zhong 2012). Furthermore, researchers have developed techniques to investigate effects of omitted (systemic) variables and these could be used to estimate ‘plausible’ and/or ‘possible’ limits of confounding (Fritz et al. 2016; Imai et al. 2010; Mauro 1990). Such sensitivity analyses investigate whether the parameter values required for change in sign or statistical significance of a model parameter of interest are mathematically possible and otherwise plausible. If desired, one could extend this line of thought to a theoretical investigation of inferential effects of complex combinations of unobserved errors and omitted variables in different biometric components (cf. Fritz et al. 2016). These further developments go beyond the present aim of establishing a useful connection between the basic mediation model and the twin design. We anticipate future research to bring a host of techniques from the mediation modeling literature into a biometric context.

The present findings should be interpreted in the light of certain other limitations. First, thus far there is less information about the detailed properties and performance of the biometric mediation model in model-selection procedures in comparison to more established related biometric models (cf. Markon and Krueger 2004; Burnham and Anderson 2004). Second, one should keep in mind the approximate nature of SLE indices. For example, our count of SLEs should reflect average differences in SLEs between individuals, but it does not exhaust all relevant life stress. The ‘true’ effect of life stress may be greater than estimated herein. In general, more work is needed towards more accurate assessment of life stress (Harkness and Monroe 2016). Third, timing of SLEs needed to be retrospectively inquired, which may introduce bias. Fourth, the classic twin design may be limited in its ability to distinguish effects of shared environment from additive genetic effects due to the correlated statistical estimators (Williams 1993 and our supplementary simulations; but see Visscher 2004). Other family-based designs might improve over the classic twin design in these respects. Fifth, although widely used and considered as a valid twin sample, the Norwegian Twin registry contains some selective attrition with respect to zygosity

and demographic and mental-health variables (Tambs et al. 2009). From the PDs, antisocial (but not borderline) PD predicted non-participation in wave 2, with non-participants having 0.09 sub-threshold criteria more than the participants (Reichborn-Kjennerud et al. 2015). We used full information maximum likelihood to minimize effects of the possible attrition bias, but some bias might remain in the estimates (Enders and Bandalos 2001). Finally, substance use counts as one of the possible “self-harming impulsive behaviors” we studied (American Psychiatric Association 2013); however, the possible construct overlap with AUD explains only part of its predictive value at most (Rosenström et al. 2018).

Although not a limitation, it is important to understand that our biometric mediation model evaluates a “phenotypic null hypothesis” which posits that it makes sense to propose and model a mediating mechanism at the level of observed phenotypes (Turkheimer et al. 2014). Rejection of this hypothesis does not preclude other types of causation. ‘True’ causal processes could be differentially transferred across biometric (ACE) components, for example, under certain gene-environment correlations and interactions (e.g., Dickens and Flynn 2001). Thus, rejection of the biometric mediation model amounts to a rejection of a certain well-defined causal hypothesis, not all conceivable causal hypotheses. This “phenotypic null hypothesis” may be a particularly important causal hypothesis in personality research, however (Turkheimer et al. 2014).

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## Compliance with ethical standards

**Conflict of interest** Tom Rosenström, Nikolai Czajkowski, Eivind Ystrom, Robert Krueger, Steven Aggen, Nathan Gillespie, Espen Eilertsen, Ted Reichborn-Kjennerud, and Fartein Torvik declare that they have no conflict of interest.

**Ethical approval** Approval was received from The Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics.

**Human and animal rights** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** A written informed consent was obtained from all participants after a complete description of the study.

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