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Prenatal smoking exposure and offspring stress coping in late adolescence: No causal link

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Abstract

Background: *In utero* exposure to tobacco smoking has been suggested to cause persistent alterations in cognitive functioning. We examined if mothers' smoking during pregnancy (SDP) is associated with long term impairment in offspring stress-coping and the causal mechanism behind a possible link.

Methods: We used a large cohort (n=187 106) of young males in Sweden (mean age=18.2 years), who underwent a semi-structured psychological assessment in 1997 to 2006, including an evaluation of stress-coping ability, as part of the compulsory military conscript examination. We compared differentially exposed siblings within nuclear families and cousins in extended families and used multilevel structural equation models to disentangle genetic from environmental contributions to the association between SDP and stress-coping.

Results: SDP and offspring stress-coping was moderately strongly associated when comparing unrelated individuals (regression coefficient (b)=-0.38 on a 9-grade scale; 95% confidence interval (CI), -0.40 – -0.36, p-value<0.0001). In contrast, it disappeared when siblings were compared (b=0.11; 95% CI, -0.01 – 0.23, p-value=0.071). This familial confounding was entirely due to genetic influences.

Conclusions: SDP is an established risk factor for pregnancy- and birth-related complications. However, we found no long-term effect of SDP on offspring stress-coping. Rather, the observed association was due to familial confounding of genetic origin; women prone to SDP also transmit genes to their children that are associated with poorer coping with stress.

Keywords: Smoking during pregnancy, adolescent stress coping, children-of-sibling model, intergenerational association.

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Introduction

Maternal smoking during pregnancy (SDP) has been linked to several negative perinatal outcomes; low offspring birth weight[1-5], preterm birth[1,4-6], spontaneous abortion,[4,5,7] and sudden infant death syndrome[4,5,7,8]. In addition, long lasting behaviour problems have been suggested; for example, compared to unrelated controls, offspring who experienced SDP have increased risk of externalizing problems[9] including attention-deficit/hyperactivity disorder,[7,9] aggression,[10] criminality,[7,11] poorer general cognitive functioning[12] and academic and intellectual performance.[13-15]

Birth-related SDP outcomes (e.g., lower birth weight, preterm birth) appear causal,[5] whereas emerging evidence suggests that the link to most studied long-term behaviours is confounded by other risks or unmeasured familial effects, such as shared environmental or genetic risks.[9,11-16]

One aspect of individual development that recently received substantial interest is the ability to cope with stress. For instance, increased stress vulnerability has been observed as a consequence of prenatal nicotine exposure in rats.[17] Animal studies also suggest that prenatal nicotine exposure increases locomotor activity and causes learning and memory problems.[7] Specifically, the foetal programming hypothesis[18,19] includes suggestions that the major regulatory systems involved in stress responses, the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, could be permanently altered early in life; both pre- and postnatally.[18,19] These alterations could, for example, be caused by restricted access to food or specific nutrients, maternal adversity, or exposure to synthetic glucocorticoids (e.g. cortisol).[19] Birth weight has often been used as a proxy for measuring adverse foetal environment,[18,19]

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and prior Swedish studies suggested that offspring size at birth is related to the measure of stress susceptibility used in the current study.[20-22]

Other possible teratogenic SDP-related mechanisms include disturbed placenta function and impaired transport of nutrients and oxygen to the foetus,[7] and nicotine-caused intrauterine hypoxia or birth asphyxia[7] leading to foetal death or long-term neurological deficits, or cellular alterations to the central and peripheral nervous systems.[7,23] The decrease in ”foetal breathing” (foetal thoracic movements), reported to occur after nicotine exposure, causes lung maturation to slow down and reduces the blood flow to the foetus.[7] Additionally, activation of neurotransmitter receptors in the foetal brain could lead to epigenetic alterations involving permanent change in cell functioning that might not be detected until much later in the more developed, adolescent, brain.[7,24]

However, another important mechanism through which SDP could effect offspring behaviour is the passing of genetic vulnerability from parent to offspring; a passive gene-environment correlation.[25] In effect, repeated results from studies of behavioural problems (e.g. externalizing behaviour,[9] criminality,[11] and poor academic achievement[14,15]) in offspring exposed to SDP were later found to be entirely confounded by familial risks. That is, a selective mechanism for SDP exposure exists so that mothers who smoke during pregnancy share also other risk factors with their children; hence, these other risk factors cause the observed adverse outcomes rather than SDP *per se*. Variables such as maternal age, education, or socioeconomic status might be the source of this selection,[7] but also unmeasured familial environment similarity and genetic risks.

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We aimed to investigate whether the association between intrauterine exposure to SDP and stress coping in Swedish late adolescent men persisted after controlling for measured and unmeasured confounding caused by intrafamilial similarity.

Methods

Study population

We linked several nation-wide longitudinal registries, maintained by government agencies in Sweden, using the unique personal identification number given to all Swedish citizens. We used data from the Multi-Generation[26] and Education Registers,[27] the 1990 Swedish Census,[28] and the Conscript,[29] Medical Birth,[30,31] Total Population, and National Crime Registers.[32] Eligible for the study were all male youth in Sweden who underwent an evaluation regarding suitability for duty by a clinical psychologist at compulsory conscription for military services during 1997-2006 and born 1982-1988 (SDP registration at antenatal care started in 1982). For this study, we used data collected regarding stress-coping (n=187 106). Military conscription was mandatory for Swedish men until 2008 and enforced by law. The majority of conscripts were 18 years old (79.3%; mean age=18.2, standard deviation (SD)=0.4, median=18.2, range 17.1-24.3 years). Individuals were linked to their siblings and cousins via parents and grandparents using the Multi-Generation Register, thus identifying extended- and nuclear families. This register links all children born 1932 or later in Sweden to both their parents. Nuclear families were indexed by the mothers (164 563 mothers with at least one child), whereas extended families were indexed by the maternal or paternal grandmother. There were 150 268 extended families with at least one individual in the offspring generation. Offspring with both maternal and paternal cousins could be included in two extended families.

Exposure

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Starting in 1982, all pregnant women in contact with public tax-funded antenatal care in Sweden are asked by their personal midwife about SDP; this information is included in the Medical Birth Register. The coverage is excellent; over 98% of all births are recorded in the register.[30] SDP data were available for 162 371 of the 187 106 (86.8%) pregnancies in the study. Of these, 44 550 women reported smoking during pregnancy (27.4%) which is comparable with earlier findings.[5,9,11,12] The validity of self-reported SDP is high in general[33] and previous studies suggest good validity also in the current sample.[2,34]

Outcome

A clinical psychologist rated individual psychological functioning (PF) at conscription, purportedly reflecting stress-coping during wartime[20,35] based on a standardized, 20-25 minute semi-structured interview. PF was rated 1-9 on a nine-point Likert-type scale; higher values indicate better coping. The distribution was stipulated to be normal with mean=5 and SD=2 (χ^2 goodness-of-fit test with 9 categories; p-value=0.23, indicating no reason to reject the normality assumption). The individual PF score was used as a proxy for general ability to cope with stress.

Covariates

We adjusted our analyses using offspring, nuclear family and extended family confounders and mediators.

Offspring confounders. Maternal age was divided into five categories; <20, 20-24, 25-29, 30-34 and >34 years. Birth year was used alone and together with Conscript Register data to stratify age at conscription into categories; ≤17.50, 17.51-18.50, and >18.50 years. A birth order variable for male nuclear family offspring was also constructed.

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Offspring mediators. We considered two mediators, both obtained from the Medical Birth Register: gestational time divided into categories; <32, 32-36, 37-41 and >41 weeks, and birth weight.

Parental confounders. Parental occupation, divided into seven categories[36], income, and cohabitation status were all based on the 1990 Census. The Register of Education for 2004 provided highest parental educational level,classified into 7 categories.[25] Parental criminal convictions for 1973-2004 were collected from the National Crime Register. The Total Population Register supplied mother's country of birth divided into 12 categories according to geographic and demographic similarities. Finally, we included a variable indicating if a half-sibship existed for offspring within the nuclear family.

Extended family confounders. We also included a variable on whether an individual had maternal or paternal half-cousins.

Statistical methods

To analyze the effect of SDP on PF, we used linear regression treating PF as a normally distributed variable. Results are presented both crude (unadjusted) and adjusted for possible confounders. To handle possible period effects, we adjusted the crude unrelated and cousin models for birth year and the crude sibling model for birth order.

Since birth weight and gestational age could be mediators of the association between SDP and PF, additional analyses were run to investigated whether these covariates mediated the association between SDP and PF as proposed by the foetal programming hypothesis.

Since we aimed at isolating a possible direct effect of SDP on PF by eliminating possible familial confounding, we ran additional models to test if familial effects distorted the

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association. With these, we compared PF in siblings and cousins differentially exposed to SDP to explore if the association remained when looking at within-family effects (i.e., if differentially exposed siblings/cousins also differed in PF). Hence, we used the extended family and nuclear family as clusters and sub-clusters to capture similarities within families. These analyses were performed with hierarchical linear models (HLM)[27,37] using SAS Proc Mixed.[38] Thus, unmeasured variables common to individuals in the nuclear or extended family (i.e., shared genes and environments) were accounted for.[9] We call this approach the Children-of-Siblings model since it is similar to the statistical methods used when examining variables for children of twins in conjunction with variables for their parents, or the Children-of-Twins model.[9,37,39,40] SDP and continuous covariates were centred around the cluster means (for both nuclear- and extended family) which yielded covariates equivalent to fixed effects.[15] Furthermore, this procedure reduced possible bias due to correlation between covariates and residual errors.[41] We utilized an informed backwards elimination process when deciding which covariates to use; thus, these may differ across models.

We performed sibling-sibling and cousin-cousin comparisons on two different data subsets. Siblings were compared using a subset consisting of two siblings within a nuclear family. Nuclear families were solely indexed by mothers, since 91% of children in Sweden stays with their mother when parents divorce or separate,[42] and our explicit aim was to capture possible familial effects. There were 26 118 individual siblings within 13 059 nuclear families. Cousin comparisons were made on a subset consisting of two cousins within an extended family. There were 52 888 individuals from 47 684 nuclear families within 26 421 extended families included in the subset (individuals eligible for comparisons within two extended families might be included twice in the analysis). To examine the difference between how SDP

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influence PF in full- and half-sibling/cousins we conducted the analyses separately. The concordance of SDP in sibling- and cousin pairs are presented in Table 1.

Insert Table 1 about here

Finally, we aimed to disentangle the source of the familial confounding of the association between maternal SDP and her boy's PF by partitioning the variance of the intergenerational association in a two-level hierarchical structural equation model (SEM) using the statistical software program Mplus.[43,44] Analyses were first performed with PF, and then on the residuals of PF retrieved from a linear regression model using the covariates. Because the results of these two analyses were very similar, we present only the analyses of the former. Results from the latter analyses are presented in the Supplemental Online Material (SOM; Figure S1). Wherever possible, we picked one pair of sisters and their children for each extended family (24 468 children from 11 485 sister-pairs). The two SEM levels refer to within-mothers, comparing the association between mothers' SDP and offspring's PF within each of the nuclear families, and between-mothers, comparing the average SDP association with the average SDP between nuclear families. The variance was partitioned into three parts *A*, *C*, and *E* corresponding to genetics, shared environment (makes siblings similar) and non-shared environment (makes siblings different)[9] (Figure 1). The partitioning of the variance comes from taking into account the genetic relatedness between the mothers; full siblings share 50% of their co-segregating genes while half-siblings share 25%. This notion was incorporated in the SEM as constraints on the genetic variance parameter modelled (V_A in Figure 1). Another constraint was that the modelled shared environment variance parameter

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V_C was equal within full sibling pairs and maternal half-siblings, whereas this parameter was set to 0 for paternal half-siblings (again, because 91% of the children remain with their mother when parents separate).[42] This way of modelling allows us to draw conclusions about which of the intergenerational paths (b_A, b_C and b_E) that explain the association between SDP and PF. The method, as applied in Children-of-Twins model, has been described elsewhere.[9,40]

Insert Figure 1 about here

Results

Mean PF scores are presented in Table 2 for SDP and offspring covariates and in Table 3 for parental covariates.

Insert Tables 2 and 3 about here

The crude estimate of the association of SDP with PF was -0.38 (95%CI, -0.40 – -0.36, p-value<0.0001; Figure 2, for results from the regression analysis: SOM Table S1). This means that a child exposed to SDP on average had a PF or stress-coping score 0.38 points lower on the nine-point scale than an unrelated child unexposed to SDP. The following analyses explored the mechanisms behind this negative association.

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Each of the included covariates individually predicted PF (analyses not shown). When adjusting for these, the association was attenuated (b=-0.15; 95%CI, -0.18 – -0.13, p-value<0.0001, Figure 2; SOM Table S2).

Having adjusted for known confounders, we investigated if the association was due to unmeasured familial confounding by performing sibling and cousin analyses with HLM. The crude and adjusted between extended family estimates ("unrelated" estimates) remained approximately similar (Figure 2). Thus, offspring in extended families where SDP had occurred also had lower mean PF scores, regardless of if a mother smoked during his own or somebody else's pregnancy (sibling's or a cousin's). As seen in Figure 2, family adjusted effects (from the sibling and cousin models) differed from "unrelated" effects. When accounting for covariates for SDP-discordant siblings, the within regression effect of SDP on PF completely disappeared (b=0.13; 95%CI, -0.01 – 0.27, p-value=0.068, Figure 2), providing strong evidence for familial confounding. Another way to address the mechanism behind this would be to study also half-siblings, but because of too few half-siblings discordant for SDP (59 pairs, Table 1) the statistical power was minimal (SOM Table S6). When full cousins were studied, the adjusted within regression parameter was close to zero (b=-0.05; 95%CI, -0.11 – 0.01, p-value=0.073, Figure 2) and reduced compared to the within half-cousins effect (b=-0.23; 95%CI, -0.44 – -0.02, p-value=0.030, Figure 2) and to the between extended family parameter, again indicating substantial familial confounding. For full tables of regression coefficients from sibling and cousin analyses see SOM Tables S3-S10.

We found minimal influence of birth weight and gestational age on the association between SDP and PF, suggesting that these covariates did not mediate neither the crude nor the

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adjusted association that we could verify. This held true for unrelated comparisons as well as sibling and cousin comparisons (analyses not shown).

Insert Figure 2 about here

Because the HLM analyses indicated substantial familial confounding, we tried to estimate genetic and environmental effects on the association using SEM. When fitting the *ACE* model, both the intergenerational paths b_C and b_E had very large standard errors (b_A=-1.48, standard error (SE)=0.90, p-value=0.10, b_C=-1.31, SE=2.65 p-value=0.62; b_E=0.18, SE=0.41 p-value=0.66), which indicates that one latent variance parameter in the model is negligible.[40] To test whether the *ACE* model fitted the data better than the *AE*- and/or the *CE* model, two scaled-difference χ^2-tests[45] were performed. We found no evidence that the *ACE* model explained the data better than the *AE* model (χ^2=1.2, degrees of freedom=2, p-value=0.56). In contrast, when comparing the *ACE* model with the *CE* model the result was in favour of the *ACE* model (χ^2=11.2, df=2, p-value=0.004). We used the Bayesian Information Criterion (BIC) to determine which of the models *ACE* and *AE* that fitted the data best. The *AE* model outperformed the *ACE* (BIC_{AE}=126 493, BIC_{ACE}=126 511; The Akaike Information Criterion (AIC) yielded a similar result: AIC_{AE}=126 277, AIC_{ACE}=126 280). Therefore, in subsequent models the shared environment parameters were set to zero.[9,40] Results from the model fitting are presented in Figure 3. The regression coefficient b_A expressing the genetic intergenerational transmission on PF was negative (b_A=-1.44, SE=0.13, p-value<0.0001) while the non-shared environmental regression coefficient was positive (b_E=0.44, SE=0.21, p-value=0.037). For the full model, see SOM Figure S2.

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Insert Figure 3 about here

Discussion

We aimed to investigate the effect of intrauterine exposure to SDP on offspring stress-coping in late adolescence. We used nation-wide longitudinal registers to compare not only unrelated individuals differentially exposed to SDP, but also relatives (siblings and cousins) to explore possible familial confounding and estimate the roles of genetic and environmental determinants.

Our main finding was that the observed association between SDP and poorer PF was entirely confounded by familial factors. Since the association could not be entirely explained by selected *à priori* confounders, we applied models that investigated unmeasured confounding based on similarities within nuclear and extended families. Familial confounding was evident; the association between SDP and poorer offspring stress-coping decreased when half-cousin comparisons were used instead of unrelated individuals, and disappeared completely in within full cousin- and full sibling comparisons. A possible reason for mothers to change smoking habits between pregnancies is if a life-altering event has occurred. However a Swedish study on whether smoking habit changes after an adverse pregnancy outcome found only modest effects on continued smoking in next pregnancy.[46] Thus, this is probably not a major reason for the familial confounding, especially since such effects are even less influential in the comparison between smoking discordant sisters. Additionally, data suggested that genetic effects entirely accounted for this familial confounding. The present results concur with previous studies in humans suggesting that associations between SDP and cognitive/behavioural outcomes in adolescent offspring are not causal but subject to

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substantial familial confounding,[9,11-15] primarily due to genetic rather than environmental mechanisms. One possible mechanism is that mothers transmit smoking liability to offspring and offspring smoking influenced stress reactivity. We could not test this since no data on smoking were available for the conscripts. Regardless, to be informative, studies of the effect of SDP and other parental risk factors on offspring must take familial confounding into account.

We also tested the foetal programming hypothesis, the study of which often used low birth weight as a proxy for adverse foetal environment.[18,19] When comparing siblings or cousins differently exposed to SDP, the inclusion of birth weight as a potential mediator of the link between SDP and offspring PF, the latter remained essentially unchanged. Thus, either the lowering of birth weight due to SDP is not in the same causal pathway as the effect on PF or the effect of low birth weight on PF is also due to familial confounding.

Our study had several strengths, particularly its size and longitudinal total population-based design with high coverage of exposure data and outcome. As supported by Swedish data, we assumed that children are primarily raised by their biological mothers when parents divorce or separate.[42] Since PF was assessed by professionals employed by the Swedish armed forces, the rating was classified. Hence, although previous studies used PF as a stress-coping measure,[20-22,35] we could not explicitly validate it. As indirect support, however, the test has been used for several decades, and it has been validated in that it correlates with military rank at the completion of military service.[47] Regarding exposure, we used mothers' smoking status at prenatal care registration (approximately the first trimester) as SDP measure. Self-reported SDP might be less reliable in later years, since the stigma associated with smoking while pregnant has increased. However, studies support its validity,[2,33,34] the period when SDP was

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measured was quite short (1982-1988), and we controlled for period effects when including birth year/birth order as a covariate. We cannot differentiate between prenatal only and prenatal plus postnatal smoking; therefore, the associations examined could be due to postnatal smoking as well as SDP. Another limitation of the study is that analyses was done in men, hence generalization to women cannot be assumed.

Finally, we want to stress that mothers' smoking during pregnancy is associated with numerous adverse outcomes, especially related to birth and infancy.[5,48] However, our results add to the accumulating evidence that smoking during pregnancy have no, or only minor, long-term causal effects on offspring cognitive functioning.[9,11-15] Other factors accounts for the association, and in the case of stress-coping the confounds seem to be mainly of genetic origin. To conclude, mothers prone to SDP also transmit genes to their children, which cause poorer stress coping in the latter.

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Key messages

- Foetal exposure to tobacco smoking is suggested to cause long term alterations to regulatory systems involved in stress response.
- We found an association between smoking during pregnancy and worse stress coping in male offspring at 18 years of age.
- This association is not causal but subject to substantial familial confounding
- The familial confounding seems to be primarily of genetic origin.

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Table 1. Concordance regarding exposure to maternal smoking during pregnancy in sibling- and cousin pairs among all male children born 1982-1988 in Sweden and assessed for psychological functioning at age 18 as part of mandatory military conscript evaluation

Relation	**SDP = 0**	**SDP = 1**	**Total**
Full siblings			25 452
Concordant	18 702	4450	23 152
Discordant	1150	1150	2300
Half siblings			666
Concordant	256	292	548
Discordant	59	59	118
Full cousins			50 038
Concordant	27 480	5106	32 586
Discordant	8726	8726	17 452
Half cousins			2850
Concordant	978	492	1470
Discordant	690	690	1380

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Table 2. Offspring characteristics for all 187 106 male children born 1982-1988 in Sweden and assessed for psychological functioning at age 18 as part of mandatory military conscript evaluation

Characteristic	**n (%)**	**Psychological functioning Mean (SD)**
Smoking during pregnancy		
Yes	44 550 (23.8)	4.6 (1.8)
No	117 822 (63.0)	5.0 (1.8)
Missing	24 734 (13.2)	4.9 (1.8)
Gestational time, weeks		
28-31	654 (0.3)	4.5 (1.7)
32-36	8966 (4.8)	4.8 (1.8)
37-41	162 873 (87.4)	4.9 (1.8)
>41	13 812 (7.4)	4.9 (1.8)
Missing	801 (0.4)	4.7 (1.7)
Age at conscription, years		
≤17.50	2245 (1.2)	5.0 (1.7)
17.51-18.50	158 625 (84.8)	4.9 (1.8)
>18.50	26 236 (14.0)	4.6 (1.9)
Year of birth		
1982	29 971 (16.0)	4.8 (1.8)
1983	28 231 (15.1)	4.9 (1.8)
1984	25 915 (13.9)	5.1 (1.7)
1985	30 243 (16.2)	4.8 (1.9)

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1986	27 017 (14.4)	4.8 (1.8)
1987	25 801 (13.8)	4.7 (1.8)
1988	19 928 (10.7)	4.9 (1.7)
Birth order		
1	169 702 (90.7)	4.9 (1.8)
2	16 812 (9.0)	4.9 (1.8)
3	578 (0.3)	4.8 (1.8)
4	10 (0.0)	4.5 (1.5)
5	1 (0.0)	7 (-)
Missing	3 (0.0)	4.3 (2.1)
Birth weight, kilograms		
<1.50	1641 (0.9)	4.7 (1.7)
1.50-1.99	1006 (0.5)	4.6 (1.8)
2.00-2.49	3503 (1.9)	4.6 (1.8)
2.50-2.99	16 233 (8.7)	4.7 (1.8)
3.00-3.49	55 210 (29.5)	4.8 (1.8)
3.50-3.99	68 784 (36.8)	4.9 (1.8)
≥4	40 729 (21.8)	4.9 (1.8)
Mother's age at delivery, years		
<20	5491 (2.9)	4.3 (1.8)
20-24	43 338 (23.2)	4.7 (1.8)
25-29	69 977 (37.4)	4.9 (1.8)
0-34	47 551 (25.4)	5.0 (1.8)
>34	20 749 (11.1)	4.9 (1.8)

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Total	187 106	4.9 (1.8)

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Table 3. Characteristics for parents of all 187 106 male children born 1982-1988 in Sweden and assessed for psychological functioning at age 18 as part of mandatory military conscript evaluation.

	Maternal characteristics		**Paternal characteristics**	
Characteristic	**n (%)**	**Psychological functioning Mean (SD)**	**n (%)**	**Psychological functioning Mean (SD)**
Parent's occupation				
Unskilled blue collar worker	48 941 (26.2)	4.6 (1.7)	34 349 (18.4)	4.6 (1.8)
Skilled blue collar	20 845 (11.1)	4.8 (1.7)	37 737 (20.2)	4.7 (1.7)
Low level white collar	28 390 (15.2)	5.0 (1.7)	16 086 (8.6)	5.0 (1.8)
Intermediate level white collar	36 426 (19.5)	5.2 (1.8)	32 521 (17.4)	5.1 (1.8)
High level white collar	13 395 (7.2)	5.3 (1.8)	28 976 (15.5)	5.2 (1.8)
Self employed	5615 (3.0)	5.0 (1.8)	14 889 (8.0)	4.9 (1.8)
No information/uncategorized	10 576 (5.7)	4.7 (1.8)	9692 (5.2)	4.7 (1.8)
Missing[†]	22 918 (12.2)	4.6 (1.8)	12 856 (6.9)	4.5 (1.8)
Parent's income, Swedish kronor				
<100 000	91 964 (49.2)	4.7 (1.8)	25 538 (13.6)	4.5 (1.8)
100 000-199 900	89 125 (47.6)	4.9 (1.8)	96 755 (51.7)	4.7 (1.8)
200 000-299 900	5194 (2.8)	5.4 (1.8)	50 536 (27.0)	5.1 (1.8)
300 000-399 900	686 (0.37)	5.4 (1.8)	10 059 (5.4)	5.4 (1.7)

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≥400 000	137 (0.07)	5.6 (2.0)	4218 (2.3)	5.6 (1.8)
Parent's highest education at childbirth				
Less than 9 years	4179 (2.2)	4.3 (1.8)	10 649 (5.7)	4.5 (1.7)
9 years	17 955 (9.6)	4.4 (1.8)	26 099 (13.9)	4.6 (1.7)
1-2 years upper secondary education	67 436 (36.0)	4.7 (1.7)	61 131 (32.7)	4.7 (1.8)
3 years upper secondary education	23 762 (12.7)	4.9 (1.8)	23 859 (12.8)	5.0 (1.8)
<3 years post-secondary education	33 622 (18.0)	5.1 (1.8)	25 175 (13.5)	5.2 (1.8)
3+ years post-secondary education	36 056 (19.3)	5.2 (1.8)	29 013 (15.5)	5.2 (1.8)
Postgraduate education	992 (0.5)	5.3 (1.9)	2862 (1.5)	5.2 (1.8)
Missing	3104 (1.7)	4.5 (1.9)	8318 (4.4)	4.5 (1.9)
Parent convicted of a criminal offense‡				
No	167 303 (89.4)	4.9 (1.8)	117 597 (62.9)	5.0 (1.8)
Yes	19 803 (10.6)	4.5 (1.8)	69 509 (37.1)	4.6 (1.8)
Mother's country of birth				
Sweden	170 017 (90.9)	4.9 (1.8)	n/a	n/a
Scandinavia except Sweden	7466 (4.0)	4.6 (1.8)	n/a	n/a
25 European Union member states except Scandinavia and former	1367 (0.7)	4.7 (1.8)	n/a	n/a

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Eastern Europe				
Former Eastern Europe	1745 (0.9)	4.7 (1.9)	n/a	n/a
Europe except Scandinavia, 25 European Union member states and former Eastern Europe	2439 (1.3)	4.4 (1.7)	n/a	n/a
Former USSR	113 (0.1)	4.6 (1.8)	n/a	n/a
Africa	507 (0.3)	4.4 (1.6)	n/a	n/a
Canada or USA	261 (0.1)	4.7 (1.9)	n/a	n/a
Rest of North America	64 (0.0)	4.7 (1.8)	n/a	n/a
South America	814 (0.4)	4.4 (1.7)	n/a	n/a
Asia	2165 (1.2)	4.3 (1.7)	n/a	n/a
Oceania	35 (0.0)	4.5 (1.4)	n/a	n/a
Missing	113 (0.1)	4.7 (1.7)	n/a	n/a
Half-sibship[§]			n/a	n/a
No	186 157 (99.5)	4.9 (1.8)	n/a	n/a
Yes	949 (0.5)	4.5 (1.8)	n/a	n/a
Cohabitation status			n/a	n/a
Parents cohabiting	159 102 (85.0)	4.9 (1.8)	n/a	n/a
Parents not cohabiting	7998 (4.3)	4.5 (1.8)	n/a	n/a
Missing	20 006 (10.7)	4.9 (1.8)	n/a	n/a

[†] Missing values from the 1990 Census was due to that some Swedes failed to respond as required by law.

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[‡] Criminal convictions were obtained from the national crime registry; hence, there were no missing data.

[§] The low prevalence of half-siblings was due to the short time interval (7 years, 1982-1988) during which both the index children and the half siblings had to be born, and that only male children with a score for psychological functioning at conscription were included.

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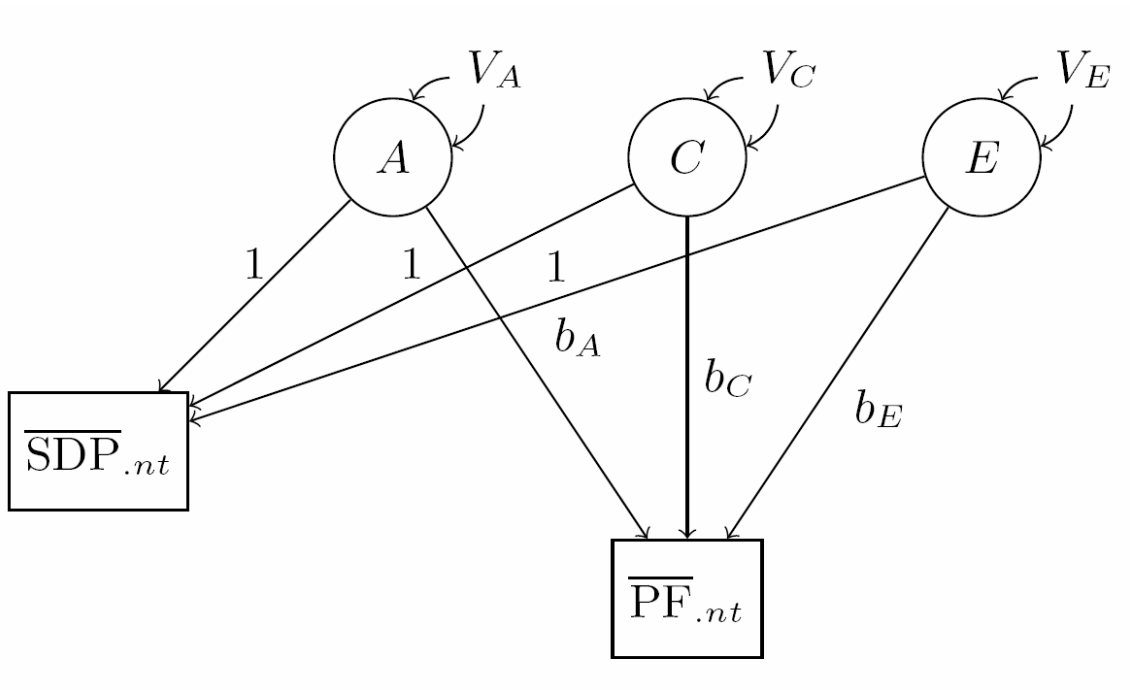

Figure 1. Variance partitioning for *A*, genetics; *C*, the shared environment; and *E*, non-shared environment. The graph represents the model for one of two sibling mothers. SDP = mean smoking during pregnancy exposure, PF = mean psychological functioning capacity (stress coping), *A* = latent variable representing the genes, *C* = latent variable representing the shared environment, *E* = latent variable representing the non-shared environment, V_A = variance of latent variable *A*, V_C = variance of latent variable *C*, V_E = variance of latent variable *E*, b_A = regression coefficient for PF regressed on *A*, b_C = regression coefficient for PF regressed on *C*, b_E = regression coefficient for PF regressed on *E*.

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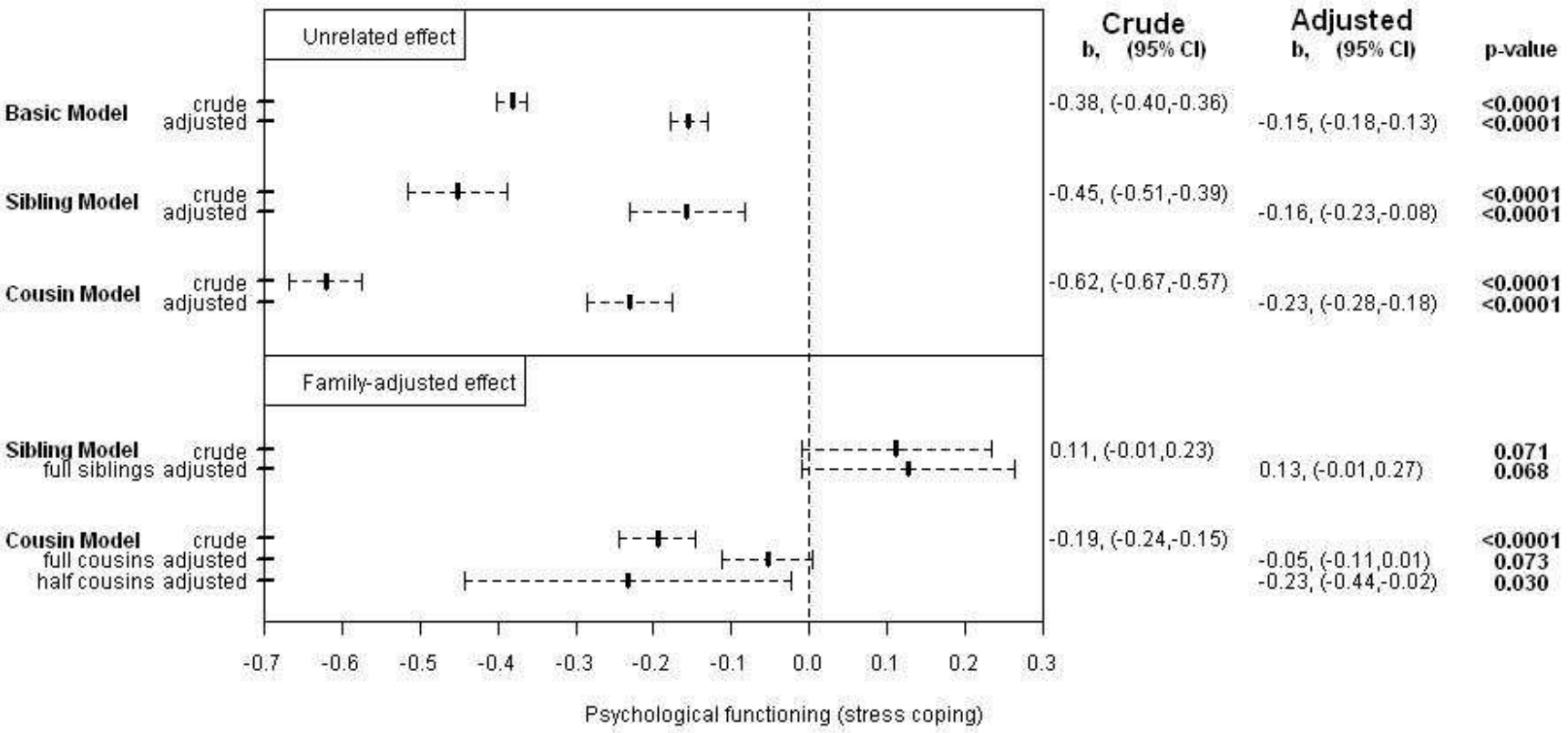

Figure 2. Regression coefficient estimates and 95% confidence intervals for psychological functioning as a function of maternal smoking during pregnancy among male offspring born 1982-1988 in Sweden and assessed for psychological functioning at age 18 as part of mandatory military conscript evaluation.

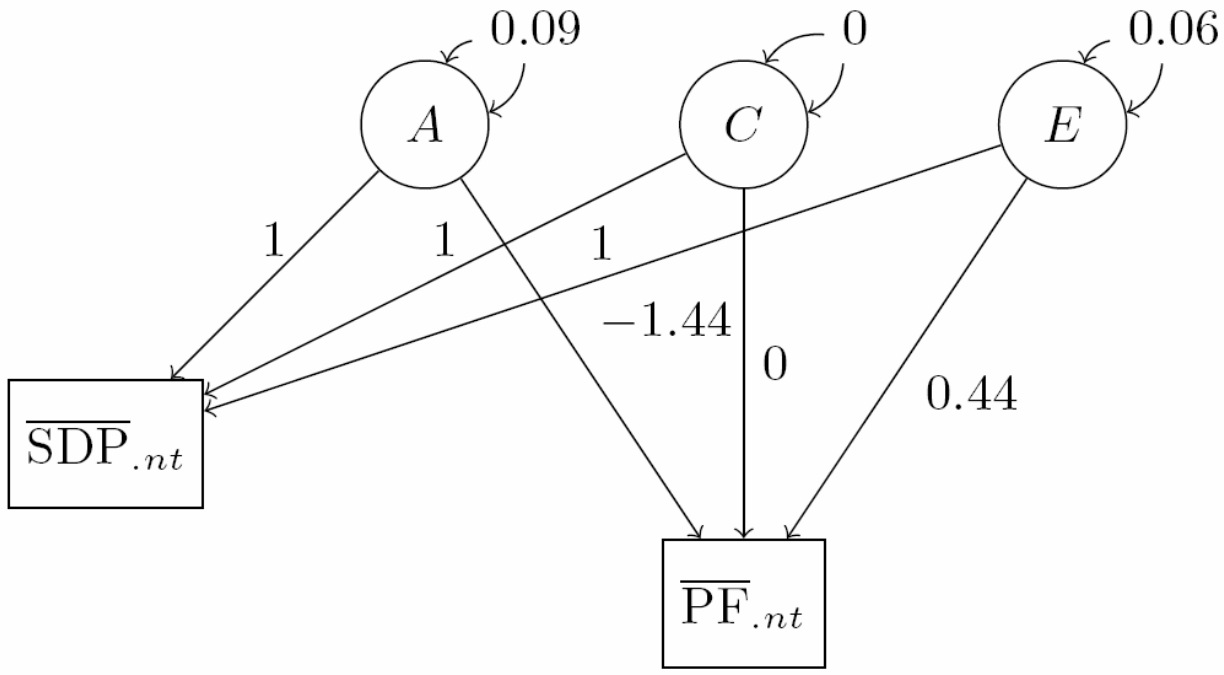

Figure 3. Variance partitioning for *A*, genetics; *C*, the shared environment; and *E*, non-shared environment. The graph represents the fitted model for one of two sibling mothers. SDP = mean smoking during pregnancy exposure, PF = mean psychological functioning capacity (stress coping), *A* = latent variable representing the genes, *C* = latent variable representing the shared environment, *E* = latent variable representing the non-shared environment, variance of latent variable *A* = 0.09 (p-value<0.0001), variance of latent variable *E* = 0.06 (p-value<0.0001), regression coefficient for PF regressed on *A* = -1.44 (p-value<0.0001), regression coefficient for PF regressed on *E* = 0.44 (p-value=0.037).

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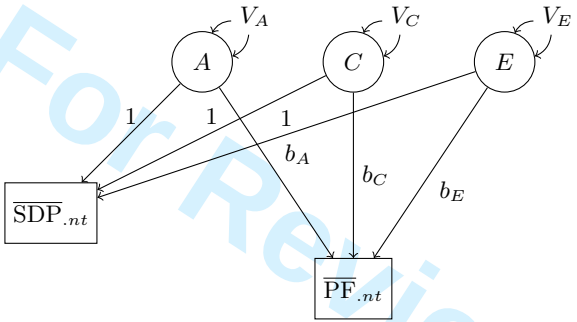

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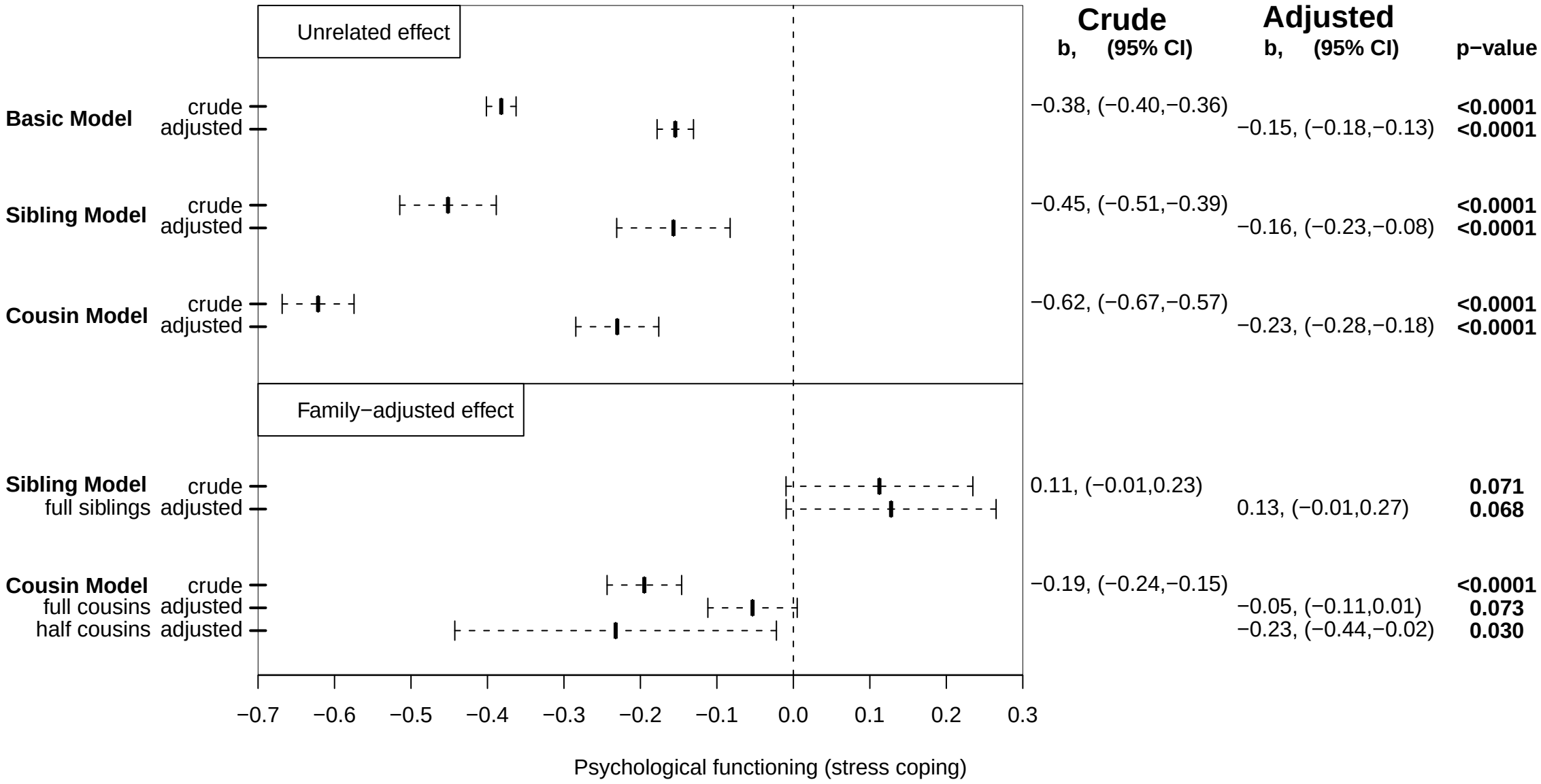
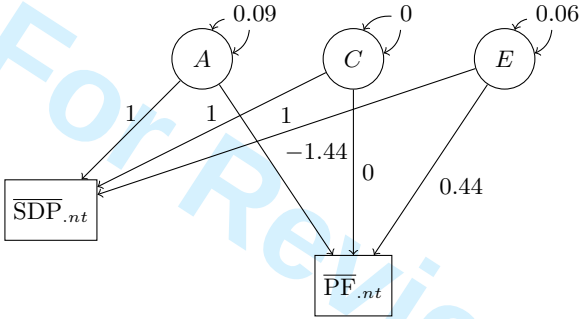

Unrelated effect
Family−adjusted effect
Crude
b, (95% CI)
Adjusted
b, (95% CI)
p−value
Basic Model
crude
adjusted
−0.38, (−0.40,−0.36)
<0.0001
−0.15, (−0.18,−0.13)
<0.0001
Sibling Model
crude
adjusted
−0.45, (−0.51,−0.39)
<0.0001
−0.16, (−0.23,−0.08)
<0.0001
Cousin Model
crude
adjusted
−0.62, (−0.67,−0.57)
<0.0001
−0.23, (−0.28,−0.18)
<0.0001
Sibling Model
full siblings
crude
adjusted
0.11, (−0.01,0.23)
0.071
0.13, (−0.01,0.27)
0.068
Cousin Model
full cousins
half cousins
crude
adjusted
adjusted
−0.19, (−0.24,−0.15)
<0.0001
−0.05, (−0.11,0.01)
0.073
−0.23, (−0.44,−0.02)
0.030
−0.7
−0.6
−0.5
−0.4
−0.3
−0.2
−0.1
0.0
0.1
0.2
0.3
Psychological functioning (stress coping)



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