

Adult aggressive behavior in humans and biomarkers:

a focus on lipids and methylation

Fiona A. Hagenbeek^{1,2*}, Jenny van Dongen^{1,2}, Cornelis Kluit³, Thomas Hankemeier^{4,5}, Lannie Ligthart¹, Gonneke Willemsen¹, Eco J.C. de Geus^{1,2,6}, Jacqueline M. Vink⁷, Meike Bartels^{1,2,6} and Dorret I. Boomsma^{1,2,6*}

¹Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands.

²Amsterdam Public Health research institute, Amsterdam, the Netherlands.

³Good Biomarker Sciences, Leiden, the Netherlands.

⁴Division of Analytical Biosciences, Leiden Academic Center for Drug Research, Leiden University, Leiden, The Netherlands.

⁵The Netherlands Metabolomics Centre, Leiden, The Netherlands

⁶Amsterdam Neuroscience, Amsterdam, the Netherlands.

⁷Behavioural Science InstituteRadboud UniversityNijmegenThe Netherlands.

*Correspondence to: Fiona A. Hagenbeek / Dorret I. Boomsma, Department of Biological Psychology,

Vrije Universiteit, Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands.

E-mail: f.a.hagenbeek@vu.nl / di.boomsma@vu.nl

Exploratory Factor Analyses

Supplementary Methods

Exploratory factor analyses (EFA) were run on the raw adult aggression data as also used in the GEE models (N=5,588). First, the factor structure of the ASR-aggression scale was investigated with EFA for categorical data using the weighted least squares with mean variance adjusted (WLSMV) estimator and using the ‘complex’ option to correct for dependency among the observations due to the inclusion of family members [1] in the software package Mplus Version 7.31 [2]. In contrast with the CBCL-Aggression Scale, the ASR-Aggression Scale does not include the items concerned with property damage (item 20 ‘damages own things’ and item 21 ‘damages others things’), therefore, the EFA analysis was repeated after including these items to the ASR-Aggression Scale items. Due to low response frequencies for the extreme response categories (see Supplementary Table S5), EFA analyses were performed after combining the highest two response categories. In these models the robust maximum likelihood (MLR) estimator was used, which uses a sandwich estimator for determining the standard errors, since Mplus interprets binary variables as continuous variables which does not support the WLSMV estimator. Finally, we investigated whether including the lipids, metabolic and inflammatory as items for the EFA would result in improved model fit. Within Mplus several descriptive model fit statistics are available to determine the number of common factors to include in the model. Here, model fit was assessed using the root mean square error of approximation (RMSEA) and the comparative fit index (CFI), with an RMSEA value smaller than 0.05 and a CFI value larger than 0.97 indicating a good fit [3]. The decision for a factor model was based on parsimony, the eigenvalues, interpretation of the scree plots (scree-function in the “psych” R-package) and the acceptability of the model fit (RMSEA and CFI).

Supplementary Results

The EFA including the ASR-Aggression Scale items using all three answer categories yielded a three factor model as a good fit for the fifteen items with a *RMSEA* of 0.020 (*C.I.* =0.017-0.023) and a *CFI* of 0.993 which was supported by the eigenvalues (Supplementary Table S6). In contrast the screeplot

for the eigenvalues favor a two-factor model (Supplementary Figure S1a) and while this model might be more parsimonious the fit indices for this model are poorer ($RMSEA = 0.028$ [0.026-0.031]; $CFI = 0.983$). In both the two- and the three factor model item 57 “Physically attacks people” had extremely low factor loading across all factors. Repeating the EFA without this item, yielded a 2-factor solution as a good fit for the 14 items with a $RMSEA$ of 0.030 ($C.I. = 0.028$ -0.033) and a CFI of 0.983, which is supported by both the eigenvalues (Table A2) and the scree plot (Supplementary Figure S1b), however a decrease in model fit as compared with a three-factor model including this item is observed. After including the CBCL-Aggression items concerned with ‘property destruction’ the best fit was again observed for a 3-factor model ($RMSEA = 0.021$ [0.019-0.024]; $CFI = 0.989$; Supplementary Table S6; Supplementary Figure S1c). Removing the poorly performing “physically attacks people” item did not improve model fit ($RMSEA = 0.022$ [0.020-0.025]; $CFI = 0.990$; Supplementary Table S6; Supplementary Figure S1d). Repeating these analyses after combining the highest two response categories resulted in an overall increase in the $RMSEA$ values and a deterioration of fit based on the CFI values. A comparison of the model fit of the preferred models by the eigenvalues (Supplementary Table S6) and the screeplots (Supplementary Figures S1g-j) can be found in Supplementary Table S7.

In our final EFA analyses we investigated whether inclusion of the lipids, glucose metabolism and inflammatory biomarkers to the models would improve fit or factor interpretation. As reducing the answer categories did not resolve in improved fit, EFA analyses were conducted using the original three answer categories and item 57 “physically attacks people” was retained as removing this item did not lead to improved model fit. Inclusion of the biomarkers to the ASR-Aggression scale indicated a 9-factor model based on the eigenvalues (Supplementary Table S6) or a 4-factor model based on the screeplot (Supplementary Figure S1e), adding the ‘property damaging’ items also resulted in a 9-factor model based on the eigenvalues (Supplementary Table S6) and a 4-factor model based on the screeplot (Supplementary Figure S1f). Model fit both including and excluding the ‘property damaging’ items for the four-factor model were insufficient, the 9-factor model including the ‘property damaging’ items had good model fit, while no fit indices could be generated for larger than

7-factor models when excluding these items (Supplementary Table S8). Based on an examination of the 4-factor models both including and excluding the ‘property damaging’ items and the 9-factor model including the ‘property damaging’ items, we conclude that adding the lipids, glucose metabolism and inflammatory biomarkers to the model does not increase model fit. Furthermore, investigation of the OBLIQUE rotated factor loading for the four factor models indicate that, overall, these biomarkers load highly on different factors than the aggression items (Supplementary Table S9).

Supplementary References

- [1] I. Rebollo, M. H. M. de Moor, C. V Dolan, and D. I. Boomsma, “Phenotypic factor analysis of family data: correction of the bias due to dependency.,” *Twin Res. Hum. Genet.*, vol. 9, no. 3, pp. 367–376, 2006.
- [2] L. Muthén and B. Muthén, *Mplus user’s guide*, Seventh ed. Los angeles, CA, 2012.
- [3] K. Schermelleh-Engel, H. Moosbrugger, and H. Müller, “Evaluating the Fit of Structural Equation Models : Tests of Significance and Descriptive Goodness-of-Fit Measures,” *Methods Psychol. Res. Online*, vol. 8, no. 2, pp. 23–74, 2003.

Tables

Supplementary Table S1. ASR items included in the ‘Aggression Scale’

ASR item 3. Argues a lot

ASR item 5. Blames others

ASR item 16. Mean to others

ASR item 28. Get along badly with family

ASR item 37. Gets into many fights

ASR item 55. Moods swing between elation and depression

ASR item 57. Physically attacks people

ASR item 68. Scream or yells a lot

ASR item 81. Behavior is very changeable

ASR item 86. Stubborn, sullen or irritable

ASR item 87. Moods or feelings change suddenly

ASR item 95. Quick temper

ASR item 97. Threatens to hurt people

ASR item 116. Gets upset too easily

ASR item 118. Is too impatient

Supplementary Table S2: Sex, age and smoking effects on Aggression

	N	Estimate	Robust SE	P-value
ASR Aggression scale sum score				
Smoking status	5,538	-0.278	0.056	8.90E-07
Sex	5,538	0.444	0.084	1.07E-07
Age blood sampling	5,538	-0.026	0.003	2.98E-18
ASR Aggression Scale case/control status (age- and gender specific cut-off of T=65)				
Smoking status	5,538	-0.2374	0.0620	0.0001
Sex	5,538	0.1739	0.1068	0.1034
Age blood sampling	5,538	0.0041	0.0037	0.2592

Note: Estimates from a generalized estimation equation (GEE) model with ASR aggression score as outcome and age and sex as predictors.

Supplementary Table S3. GEE results for the association of anthropometric traits with aggressive behavior.

	N	Estimates				Robust SE				P-value*			
		Aggression	Sex	Age ^a	Smoking	Aggression	Sex	Age ^a	Smoking	Aggression	Sex	Age ^a	Smoking
ASR Aggression scale sum score													
Weight	5522	-0.0394	12.3775	0.1701	-0.3452	0.0570	0.3751	0.0125	0.2343	0.490	7.93E-239	3.67E-42	0.141
Waist circumference	5495	-0.0279	-8.5152	0.3297	-0.7948	0.0494	0.3133	0.0108	0.1976	0.572	1.07E-162	1.01E-203	5.75E-05
Hip circumference	5488	-0.0289	-0.0430	0.0871	0.0358	0.0387	0.2250	0.0083	0.1507	0.455	0.849	1.59E-25	0.812
BMI	5513	0.0030	-0.3384	0.0859	-0.1142	0.0184	0.1112	0.0039	0.0748	0.870	0.002	1.23E-107	0.127
WHR	5485	0.0001	-0.0818	0.0025	-0.0080	0.0003	0.0021	0.0001	0.0012	0.828	0	2.46E-246	5.98E-11
Height	5529	-0.0520	12.8523	0.1028	-0.0173	0.0290	0.1970	0.0062	0.1117	0.073	0	2.28E-61	0.877
ASR Aggression Scale case/control status (age- and gender specific cut-off of T=65)													
Weight	5522	-0.3354			-1.6765	0.6879			0.2599	0.626			1.12E-10
Waist circumference	5495	0.1344			-2.4094	0.6031			0.2262	0.824			1.71E-26
Hip circumference	5488	0.2640			-0.2472	0.4082			0.1488	0.518			0.097
BMI	5513	0.1055			-0.4196	0.2062			0.0757	0.609			3.04E-08
WHR	5485	0.0003			-0.0208	0.0043			0.0016	0.944			2.83E-39
Height	5529	-0.7259		0.0696	-0.6879	0.4442		0.0086	0.1665	0.102		7.34E-16	3.59E-05

* all anthropometric traits are analyzed in an exploratory fashion. P-value threshold corrected for multiple testing is $p \leq 0.004$.

Supplementary Table S4. GEE results for the association of biomarker levels with dichotomized aggressive behavior

	N	Estimates			Robust SE			P-value*		
		Aggression	Smoking	BMI	Aggression	Smoking	BMI	Aggression	Smoking	BMI
Hba1c	4988	0.018	-0.033	0.014	0.024	0.010	0.002	0.4641	0.0006	1.07E-13
Glucose	5035	0.011	-0.075	0.040	0.026	0.010	0.002	0.6628	4.88E-15	4.36E-79
Insulin	4935	-0.026	-0.022	0.063	0.026	0.011	0.002	0.3246	0.0417	8.38E-192
Total cholesterol	4958	0.035	-0.156	0.053	0.051	0.019	0.004	0.4856	1.21E-15	8.63E-43
LDL	4953	0.043	-0.108	0.051	0.045	0.018	0.004	0.3490	1.40E-09	1.21E-45
HDL	4958	0.017	0.019	-0.026	0.018	0.007	0.001	0.3393	0.0063	2.51E-89
HDL to total cholesterol ratio	4957	0.003	0.012	-0.008	0.004	0.002	0.000	0.5433	1.27E-13	1.89E-141
LDL to HDL ratio	4952	-0.003	-0.142	0.081	0.046	0.019	0.004	0.9484	8.22E-14	1.50E-101
Triglycerides	4951	-0.019	-0.093	0.040	0.022	0.009	0.002	0.3965	2.18E-27	5.03E-126
CRP	5100	-0.076	-0.074	0.103	0.053	0.020	0.004	0.1492	0.0002	3.10E-161
Fibrinogen	4973	0.024	-0.042	0.051	0.033	0.013	0.002	0.4670	0.0011	3.24E-94
TNF- α	5047	-0.019	-0.011	0.016	0.027	0.011	0.002	0.4860	0.3255	4.54E-13
IL-6	5040	-0.024	-0.123	0.050	0.033	0.012	0.002	0.4639	3.52E-24	2.66E-110
sIL-6R	5064	-177.872	-81.677	335.100	546.636	209.098	43.011	0.7449	0.6961	6.65E-15
HOMA2-B	4570	-0.025	0.015	0.022	0.015	0.006	0.001	0.1073	0.0132	1.73E-65
HOMA2-S	4570	0.031	0.019	-0.052	0.023	0.009	0.002	0.1672	0.0383	1.36E-166
HOMA2-IR	4570	-0.031	-0.018	0.052	0.023	0.009	0.002	0.1703	0.0450	1.54E-167

* p-value threshold corrected for multiple testing for the confirmatory analyses (includes: CRP, LDL, IL6, LDL:HDL ratio, HDL:CHOL ratio and HDL) is $p \leq 0.01$ and $p \leq 0.004$ for the exploratory analyses (anthropometric traits, fibrinogen, insulin, glucose, HOMA2S, HOMA2IR, HOMA2B, hba1c, sIL-6R, TNF- α and triglycerides).

Supplementary Table S5. Frequencies of the ASR aggression item responses for all three answer categories versus only two answer categories.

Items ^a	All categories			Two categories	
	0	1	2	0	1+2
3. Argues a lot	0.733	0.255	0.012	0.733	0.267
5. Blames others	0.835	0.158	0.007	0.835	0.165
16. Mean to others	0.892	0.102	0.006	0.892	0.108
*20. Damages or destroys own things	0.989	0.009	0.002	0.989	0.011
*21. Damages or destroys things belonging to others	0.994	0.005	0.001	0.994	0.006
28. Get along badly with family	0.862	0.121	0.017	0.862	0.138
37. Gets into many fights	0.992	0.007	0.001	0.992	0.008
55. Moods swing between elation and depression	0.814	0.163	0.023	0.814	0.186
57. Physically attacks people	0.853	0.146	0.001	0.853	0.147
68. Scream or yells a lot	0.932	0.065	0.003	0.932	0.068
81. Behavior is very changeable	0.809	0.17	0.021	.809	0.191
86. Stubborn, sullen or irritable	0.686	0.297	0.016	0.686	0.314
87. Moods or feelings change suddenly	0.769	0.213	0.017	0.769	0.231
95. Quick temper	0.87	0.125	0.005	0.870	0.130
97. Threatens to hurt people	0.994	0.005	0.001	0.994	0.006
116. Gets upset too easily	0.771	0.206	0.022	0.771	0.229
118. Is too impatient	0.591	0.376	0.033	0.591	0.409

Note: ^a = numbers refer to items numbers of the ASR

Note * = items not included in ASR-Aggression Scale

Supplementary Table S7. Model comparison for the factor structure of adult aggression after combining the extreme answer categories.

Model	Degrees of freedom	RMSEA (C.I.)	CFI
ASR-Aggression Scale			
Two factor model ^a	76	0.029 (0.026-0.032)	0.952
Three factor model ^{b,c}	NA	NA	NA
Two factor model without item57 ^a	64	0.030 (0.028-0.033)	0.953
Three factor model without item57 ^{b,c}	NA	NA	NA
ASR-Aggression Scale + property damaging items (CBCL-Aggression-Scale items)			
Two factor model ^a	103	0.037 (0.035-0.040)	0.875
Four factor model ^b	74	0.024 (0.022-0.027)	0.962
Two factor model without item57 ^a	89	0.039 (0.037-0.042)	0.874
Four factor model without item57 ^b	62	0.025 (0.022-0.028)	0.963

Notes: ^a preferred model based on screeplot.

^b preferred model based on eigenvalues.

^c fit indices could not be generated for these models as the chi-square test could not be computed for these models.

Supplementary Table S8. Model comparison for the factor structure of adult aggression after including the lipids, glucose metabolism and inflammatory biomarkers to the model.

Model	Degrees of freedom	RMSEA (C.I.)	CFI
ASR-Aggression Scale			
Four factor model ^a	374	0.051 (0.050-0.052)	0.861
Nine factor model ^{b,c}	NA	NA	NA
ASR-Aggression Scale + property damaging items (CBCL-Aggression-Scale items)			
Four factor model ^a	431	0.046 (0.045-0.047)	0.868
Nine factor model ^{b,c}	291	0.017 (0.016-0.019)	0.987

Notes: ^a preferred model based on screeplot.

^b preferred model based on eigenvalues.

^c fit indices could not be generated for these models as the chi-square test and standard errors could not be computed for these models.

Supplementary Table S9. OBLIQUE rotated factor loadings for the ASR-Aggression Scale 4-factor model including the lipids, glucose metabolism and inflammatory biomarkers.

Items	ASR-Aggression Scale				ASR-Aggression Scale with property damaging items			
					Factors			
	1	2	3	4	1	2	3	4
Hba1c	0.109	0.045	0.08	0.005	0.139	-0.016	0.074	0.004
Glucose	0.226	0.1	0.231	-0.043	0.293	-0.027	0.218	-0.041
Insulin	0.001	0.007	0.994	-0.002	0.017	-0.012	0.993	-0.003
Total cholesterol	0.959	0.032	0.034	0.007	0.914	-0.331	-0.021	0.012
LDL	0.708	0.314	-0.045	-0.002	0.908	-0.066	-0.084	0.002
HDL	0.742	-1.157	0	0.001	-0.241	-0.939	-0.054	0.01
HDL to total cholesterol ratio	-0.039	-0.952	-0.025	0.005	-0.803	-0.565	-0.027	0.01
LDL to HDL ratio	0.149	0.843	0.013	0.001	0.818	0.462	0.008	-0.002
Triglycerides	0.079	0.423	0.255	0.003	0.416	0.227	0.252	0.002
CRP	0.074	0.09	0.298	0.005	0.145	0.024	0.294	0.005
Fibrinogen	0.123	0.106	0.214	0.007	0.202	0.018	0.207	0.008
TNF- α	0.01	0.119	0.039	0.006	0.105	0.069	0.039	0.005
IL-6	0.07	0.118	0.163	-0.022	0.161	0.046	0.158	-0.022
sIL-6R	0.066	0.107	0.008	-0.023	0.147	0.04	0.004	-0.024
HOMA2B ^b	-0.187	-0.012	0.79	0.025	-0.175	0.05	0.801	0.023

Items	ASR-Aggression Scale				ASR-Aggression Scale with property damaging items			
					Factors			
	1	2	3	4	1	2	3	4
HOMA2S ^b	0.002	0.001	-0.995	0.009	-0.008	0.016	-0.994	0.009
HOMA2IR ^b	-0.003	-0.001	0.992	-0.007	0.007	-0.015	0.992	-0.007
3. ^a Argues a lot	-0.053	-0.003	0.019	0.51	-0.042	0.018	0.033	0.513
5. Blames others	0.018	-0.02	-0.006	0.469	0.008	-0.018	0.003	0.473
16. Mean to others	-0.003	0.013	0.001	0.561	0.015	0.022	0.011	0.57
*20. Damages or destroys own things	-	-	-	-	-0.056	0.483	-0.069	0.622
*21. Damages or destroys things belonging to others	-	-	-	-	-0.053	0.602	-0.04	0.696
28. Get along badly with family	0.061	0.068	-0.007	0.398	0.12	0.011	0	0.398
37. Gets into many fights	0.109	-0.004	-0.001	0.51	0.104	-0.011	0	0.518
55. Moods swing between elation and depression	0.045	-0.065	0.012	0.798	0.01	-0.088	0.032	0.798
57. Physically attacks people	-0.1	-0.046	-0.042	0.126	-0.127	0.004	-0.033	0.124
68. Scream or yells a lot	-0.047	0.041	-0.004	0.659	0	0.049	0.013	0.665
81. Behavior is very changeable	0	-0.015	0.046	0.734	0.007	-0.036	0.066	0.733
86. Stubborn, sullen or irritable	-0.077	0.043	0.008	0.721	-0.02	0.028	0.032	0.717
87. Moods or feelings change	0.049	-0.074	0.011	0.857	0.008	-0.096	0.032	0.858

Items	ASR-Aggression Scale				ASR-Aggression Scale with property damaging items			
					Factors			
	1	2	3	4	1	2	3	4
suddenly								
95. Quick temper	-0.011	0.048	-0.002	0.764	0.044	0.021	0.018	0.766
97. Threatens to hurt people	-0.062	0.191	-0.128	0.605	0.1	0.162	-0.113	0.609
116. Gets upset too easily	0.024	-0.068	-0.006	0.737	-0.015	-0.075	0.012	0.737
118. Is too impatient	-0.004	-0.006	-0.001	0.63	0.005	-0.018	0.015	0.629

Note: **bold** factor loadings are the highest loadings as observed for each item per model

^a = numbers refer to items numbers of the ASR

^b = homeostatic model assessment (HOMA) is a method to quantify insulin resistance and beta-cell function

* = items not included in ASR-Aggression Scale but in CBCL-Aggression Scale

Supplementary Table S10. Paired t-test results for confirmatory and exploratory residual biomarker levels between aggression discordant MZ twins (N = 31 pairs).

Biomarker	Low-scoring		High-scoring		Mean difference ^a	p-value ^b
	twin		twin			
	Mean	SD	Mean	SD		
Confirmatory analyses						
CRP	2.6	2.9	3.0	3.8	0.312	0.139
HDL to total cholesterol ratio	0.3	0.1	0.3	0.1	0.013	0.288
HDL	1.4	0.3	1.5	0.3	0.050	0.335
IL-6	1.3	0.9	1.8	1.4	0.183	0.373
LDL to HDL ratio	2.4	1.1	2.1	0.8	-0.156	0.383
LDL	5.2	1.1	4.9	1.0	-0.094	0.568
Total cholesterol	2.6	2.9	3.0	3.8	-0.090	0.589
Exploratory analyses						
Glucose	5.3	0.5	5.1	0.5	-0.271	0.003 ^b
Fibrinogen	2.7	0.7	3.0	0.8	0.430	0.010
Insulin	8.6	4.3	7.1	3.6	-0.136	0.130
HOMA2-S	106.4	52.5	125.1	60.6	0.123	0.180
HOMA2-IR	1.2	0.5	1.0	0.5	-0.116	0.207
Hba1c	5.3	0.4	5.4	0.5	0.165	0.297
TNF- α	0.9	0.4	0.8	0.4	-0.072	0.534
Triglycerides	1.3	0.9	1.1	0.6	-0.039	0.666
Weight	70.7	12.2	69.5	12.7	-0.505	0.726
BMI	24.4	4.4	24.0	4.6	-0.139	0.752
sIL-6R	40287.3	10963.4	41060.0	12831.3	409.067	0.820

Biomarker	Low-scoring		High-scoring		Mean difference ^a	p-value ^b
	twin		twin			
	Mean	SD	Mean	SD		
WHR	0.8	0.1	0.8	0.1	0.002	0.823
Height	170.5	6.7	170.5	7.8	-0.133	0.850
HOMA2-B	92.7	38.3	86.8	25.6	0.009	0.896
Waist circumference	80.7	11.0	80.4	11.3	0.113	0.941
Hip circumference	102.3	9.1	101.9	10.5	-0.055	0.958

^a Mean difference in residual biomarker level between aggression-discordant twins

^b Significant after correcting for multiple testing; $p \leq 0.01$ confirmatory analyses; $p \leq 0.004$ exploratory analyses

Supplementary Table S11. Paired t-test results for confirmatory and exploratory residual biomarker levels between extremely aggression discordant MZ twins (N =12).

Biomarker	Low-scoring		High-scoring		Mean difference ^a	p-value ^b
	twin		twin			
	Mean	SD	Mean	SD		
Confirmatory analyses						
CRP	2.4	3.1	3.2	3.7	1.082	0.016
LDL	3.2	1.0	2.6	0.8	-0.446	0.038
IL-6	1.5	1.0	2.4	1.7	0.785	0.045
LD to HDL ratio	2.6	1.3	1.9	0.8	-0.427	0.058
HDL to total cholesterol ratio	0.3	0.1	0.3	0.1	0.029	0.074
Total cholesterol	5.1	1.0	4.5	0.8	-0.439	0.108
HDL	1.4	0.3	1.5	0.4	0.030	0.522
Exploratory analyses						
Fibrinogen	2.6	0.8	3.0	0.8	0.669	0.008
Insulin	7.8	4.4	6.2	2.8	-0.222	0.112
Glucose	5.2	0.5	5.1	0.4	-0.156	0.189
HOMA2S	109.9	47.5	121.5	49.1	0.173	0.229
HOMA2IR	1.1	0.5	0.9	0.3	-0.161	0.273
HOMA2B	94.9	49.1	82.2	14.7	-0.071	0.564
Height	170.1	7.5	169.4	9.8	-0.986	0.568
Hba1c	5.2	0.3	5.1	0.3	-0.126	0.587
WHR	0.8	0.1	0.8	0.1	0.007	0.666
sIL-6R	36728.6	9137.6	38329.3	9363.0	1136.822	0.679
TNF- α	0.9	0.4	0.9	0.3	-0.086	0.733
Weight	69.4	10.2	67.7	12.4	-0.823	0.794

Biomarker	Low-scoring		High-scoring		Mean difference^a	p-value^b
	twin		twin			
	Mean	SD	Mean	SD		
Triglycerides	1.2	0.5	1.0	0.4	-0.029	0.836
Waist circumference	79.6	10.8	79.7	11.2	0.554	0.861
BMI	24.2	4.2	23.7	4.7	-0.080	0.929
Hip circumference	100.3	7.3	99.5	8.2	-0.167	0.947

^a Mean difference in residual biomarker level between aggression-discordant twins

^b Significant after correcting for multiple testing; $p \leq 0.01$ confirmatory analyses; $p \leq 0.004$ exploratory analyses

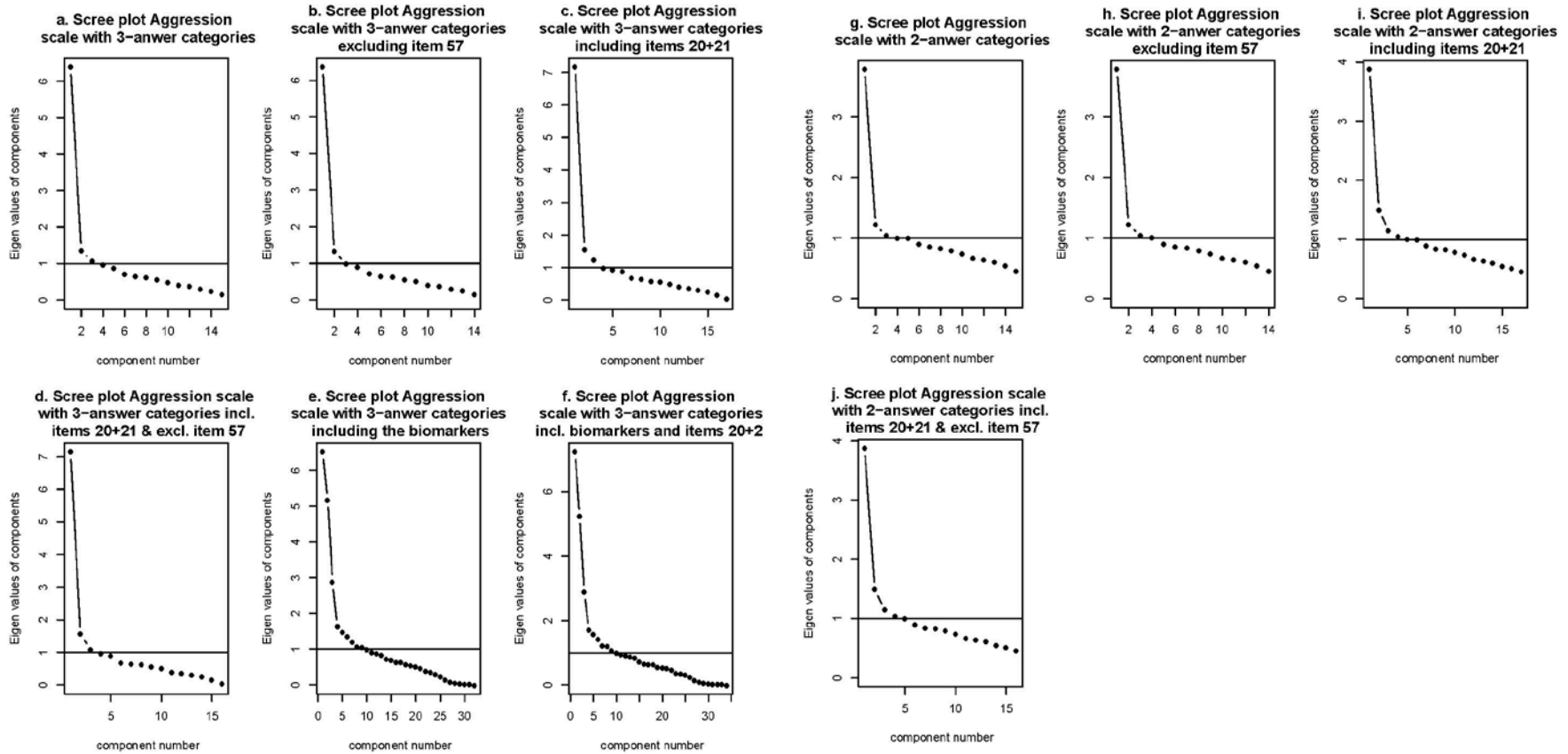
Supplementary Table S12. Aggression EWAS results for the 21 CpGs associated with lipids for the entire NTR-cohort and in aggression discordant MZ twins.

EWAS of Aggression in the entire NTR cohort				EWAS in discordant MZ twins		
cgid	Beta	RobustSE	P-value	Mean ^a diff	T-value	P-value
cg00908766	-3.27E-04	0.000632	0.604921	9.26E-05	0.01577222	0.987581
cg05575921	-1.51E-03	0.000656	0.021636	1.62E-02	0.96635195	0.346008
cg15863539	2.84E-05	0.000103	0.783301	6.13E-03	1.40734412	0.175475
cg14476101	-1.10E-04	0.000304	0.717568	-1.41E-03	-0.18689786	0.853722
cg17901584	-2.83E-04	0.000251	0.259616	-8.30E-03	-1.31870443	0.202943
cg19693031	5.33E-04	0.000246	0.03033	5.37E-03	0.65198856	0.522218
cg27168858	-1.72E-04	0.000236	0.465925	-5.34E-03	-1.2790051	0.216296
cg05119988	9.07E-05	0.000224	0.685443	-9.05E-03	-1.51111156	0.147214
cg06690548	-1.32E-04	0.000153	0.389081	9.57E-04	0.20182931	0.842195
cg06560379	1.36E-04	0.000137	0.32156	1.24E-03	0.34213424	0.736005
cg19589396	1.81E-04	0.000216	0.402031	3.15E-03	0.53869718	0.596352
cg07504977	3.78E-04	0.000233	0.103806	2.49E-03	0.58686919	0.564201
cg00574958	2.20E-04	0.000138	0.110512	1.26E-03	0.40612402	0.689189
cg11376147	-6.31E-05	0.000116	0.58488	4.13E-03	0.92444392	0.366848
cg17058475	2.63E-05	0.000182	0.884987	1.29E-02	2.00525597	0.059392
cg08857797	-3.24E-04	0.000242	0.180236	-3.77E-03	-0.46152124	0.649665
cg20544516	6.36E-05	0.000146	0.6623	-1.90E-03	-0.41549153	0.682437
cg26313301	1.47E-04	0.000107	0.169737	7.87E-03	1.71055817	0.103442
cg01881899	1.54E-04	0.000147	0.295243	5.52E-03	1.47652248	0.156186
cg06500161	-1.59E-04	0.000175	0.362525	6.96E-03	1.52102635	0.144722
cg27243685	-2.94E-04	0.000148	0.047189	-8.58E-03	-1.52065291	0.144815

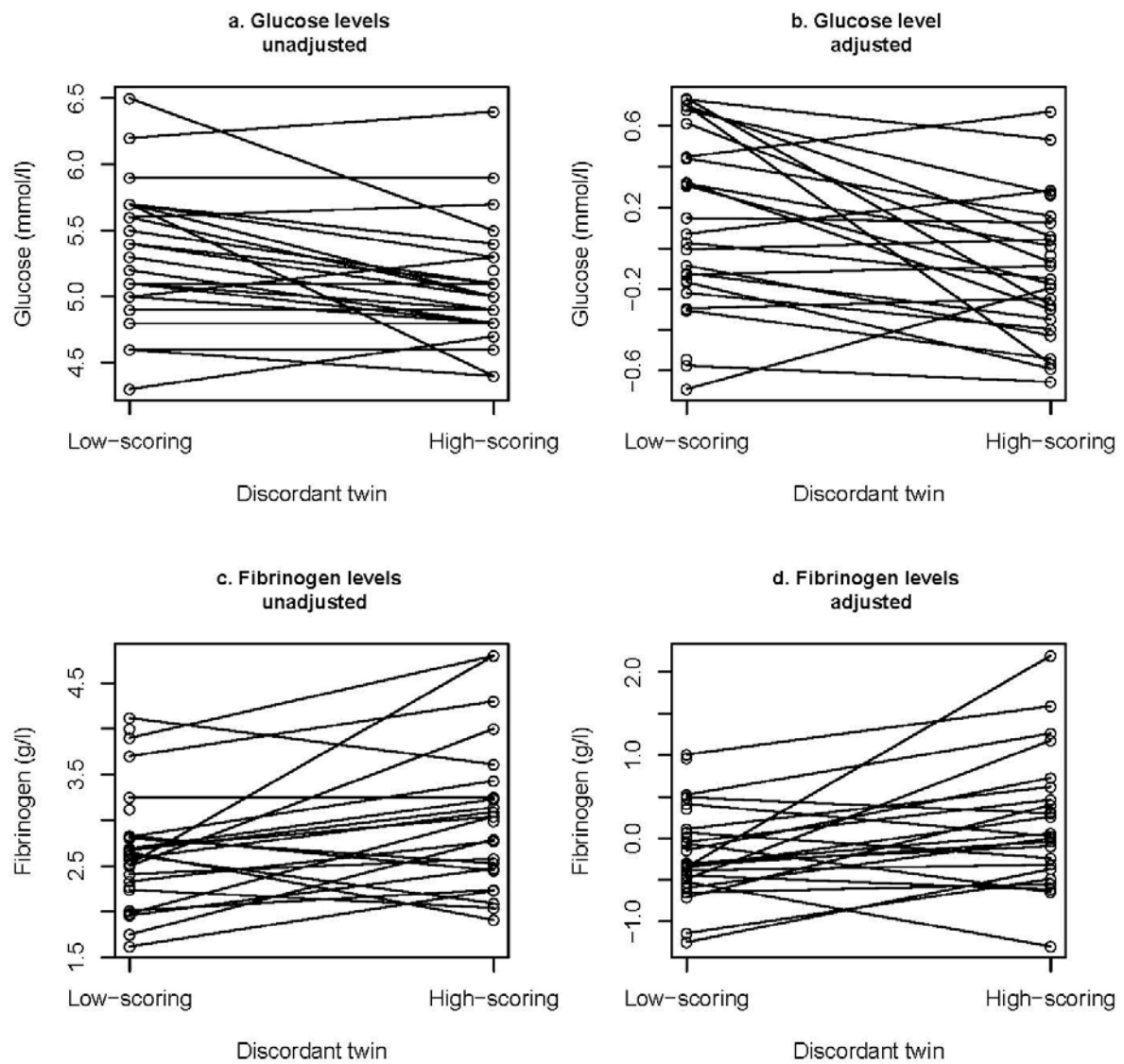
^aMean difference in residual methylation level between aggression-discordant twins (aggression high-scoring twin minus aggression low-scoring twin).

Figures

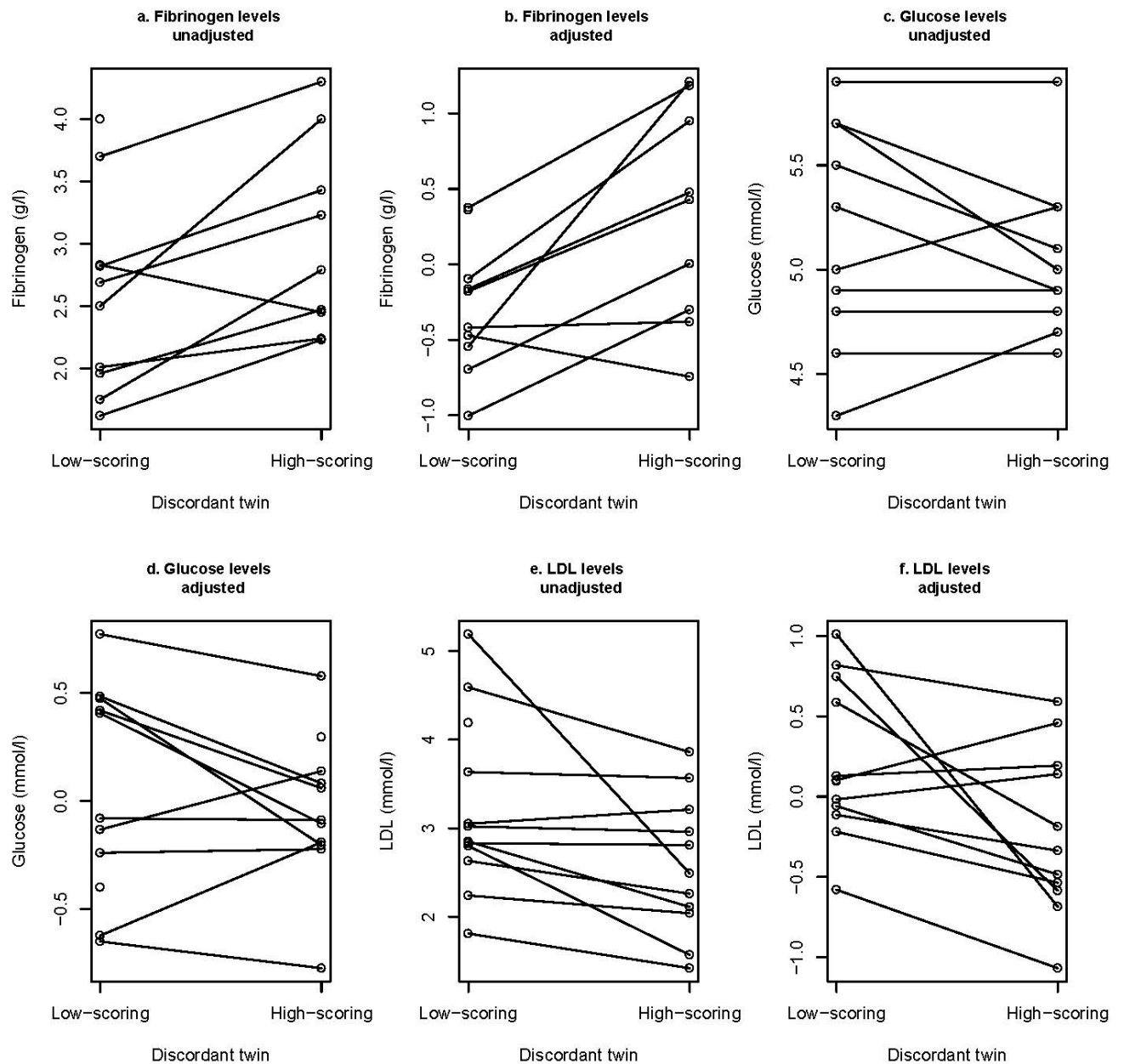
Supplementary Figures S1. Scree plots of the ASR-Aggression Scale EFA's

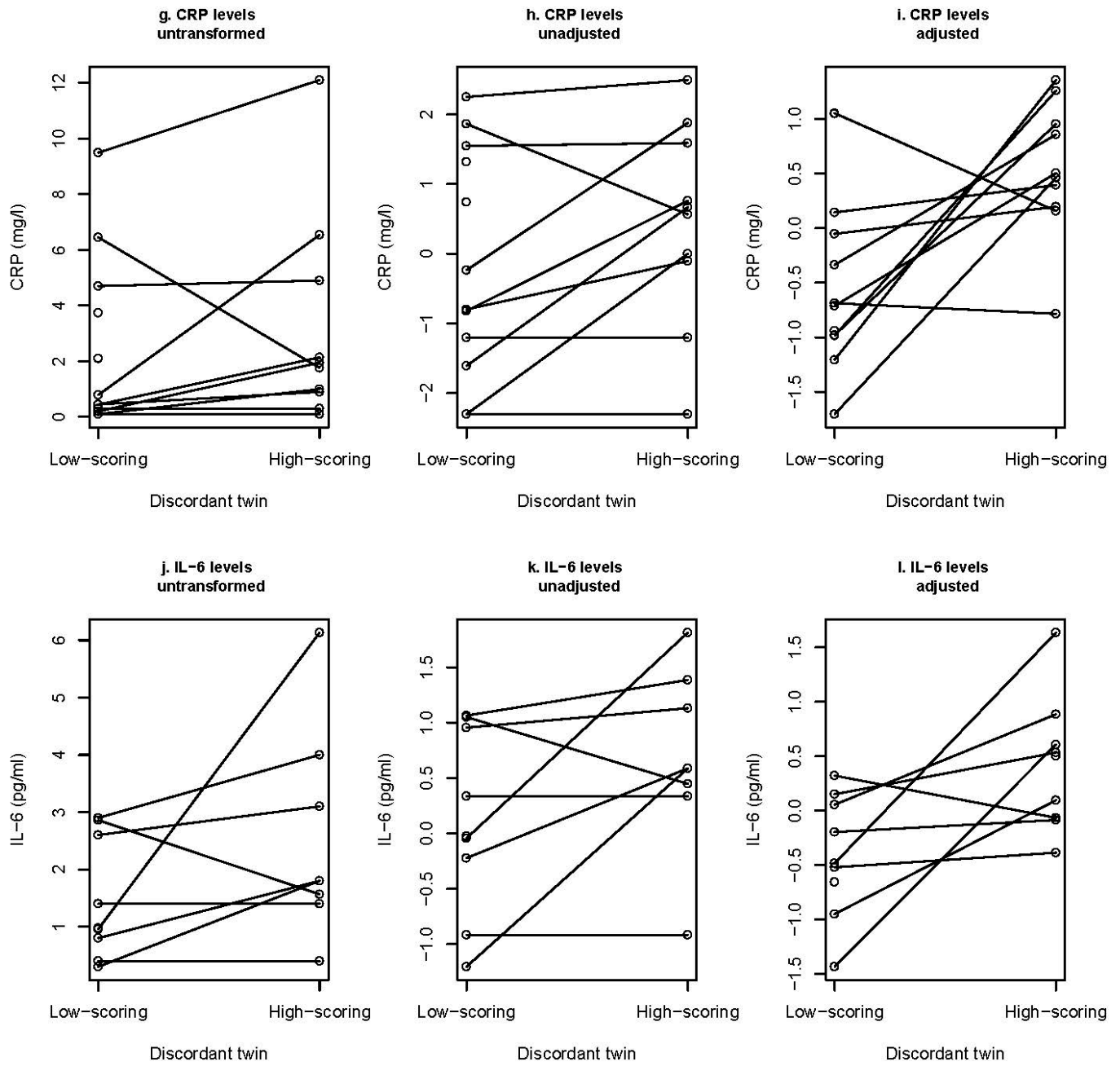


Supplementary Figure S2. Glucose and fibrinogen levels in aggression-discordant MZ twins. The unadjusted and residual biomarker levels, adjusted for covariates, are plotted for low- and high-scoring twins of 31 discordant MZ twin pairs. The biomarker levels of co-twins are connected by lines.



Supplementary Figure S3. Biomarker levels in extremely aggression-discordant MZ twins. The unadjusted and residual fibrinogen (a, b), glucose (c, d), LDL cholesterol (e, f), C-reactive protein (g, h, i) and interleukin 6 (j, k, l) levels, adjusted for covariates, are plotted for low- and high-scoring twins of 12 extremely discordant MZ twin pairs. For CRP and IL-6 the untransformed biomarker levels are also plotted. The biomarker levels of co-twins are connected by lines.





Supplementary Figure S4. QQ plots of the enrichment of lipid CpGs in the Aggression EWAS for the entire NTR cohort (a) and for the aggression discordant MZ twins (b). With the 21 CpGs significantly associated with lipids displayed in blue

