**Twin Research and Human Genetics**

**Supplementary material**

**Epigenome-wide association study of aggressive behavior**

Jenny van Dongen1,2, Michel G. Nivard1, Bart Baselmans1, Nuno R. Zilhão1, Lannie Ligthart1,

BIOS consortium3, Bastiaan T. Heijmans4, Meike Bartels1,2, Dorret I. Boomsma1,2

1 Department of Biological Psychology, VU University, Amsterdam, Van der Boechorststraat 1

1081BT, Amsterdam, The Netherlands

2 EMGO institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands

3 The Biobank-based Integrative Omics Study (BIOS) Consortium. A full list of authors is provided on the next page.

4 Department of Molecular Epidemiology, Leiden University Medical Center, Postal zone S-05-P, PO Box 9600, 2300 RC Leiden, The Netherlands

**BIOS Consortium**

**(Biobank-based Integrative Omics Study)**

**Management Team** Bastiaan T. Heijmans (chair)1, Peter A.C. ’t Hoen2, Joyce van Meurs3, Aaron Isaacs4, Rick Jansen5, Lude Franke6.

**Cohort collection** Dorret I. Boomsma7, René Pool7, Jenny van Dongen7, Jouke J. Hottenga7 (Netherlands Twin Register); Marleen MJ van Greevenbroek8, Coen D.A. Stehouwer8, Carla J.H. van der Kallen8, Casper G. Schalkwijk8 (Cohort study on Diabetes and Atherosclerosis Maastricht); Cisca Wijmenga6, Lude Franke6, Sasha Zhernakova6, Ettje F. Tigchelaar6 (LifeLines Deep); P. Eline Slagboom1, Marian Beekman1, Joris Deelen1, Diana van Heemst9 (Leiden Longevity Study); Jan H. Veldink10, Leonard H. van den Berg10 (Prospective ALS Study Netherlands); Cornelia M. van Duijn4, Bert A. Hofman11, Aaron Isaacs4, André G. Uitterlinden3 (Rotterdam Study).

**Data Generation** Joyce van Meurs (Chair)3, P. Mila Jhamai3, Michael Verbiest3, H. Eka D. Suchiman1, Marijn Verkerk3, Ruud van der Breggen1, Jeroen van Rooij3, Nico Lakenberg1.

**Data management and computational infrastructure** Hailiang Mei (Chair)12, Maarten van Iterson1, Michiel van Galen2, Jan Bot13, Dasha V. Zhernakova6, Rick Jansen5, Peter van ’t Hof12, Patrick Deelen6, Irene Nooren13, Peter A.C. ’t Hoen2, Bastiaan T. Heijmans1, Matthijs Moed1.

**Data Analysis Group** Lude Franke (Co-Chair)6, Martijn Vermaat2, Dasha V. Zhernakova6, René Luijk1, Marc Jan Bonder6, Maarten van Iterson1, Patrick Deelen6, Freerk van Dijk14, Michiel van Galen2, Wibowo Arindrarto12, Szymon M. Kielbasa15, Morris A. Swertz14, Erik. W van Zwet15, Rick Jansen5, Peter-Bram ’t Hoen (Co-Chair)2, Bastiaan T. Heijmans (Co-Chair)1.

1. Molecular Epidemiology Section, Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands

2. Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands

3. Department of Internal Medicine, ErasmusMC, Rotterdam, The Netherlands

4. Department of Genetic Epidemiology, ErasmusMC, Rotterdam, The Netherlands

5. Department of Psychiatry, VU University Medical Center, Neuroscience Campus Amsterdam, Amsterdam, The Netherlands

6. Department of Genetics, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands

7. Department of Biological Psychology, VU University Amsterdam, Neuroscience Campus Amsterdam, Amsterdam, The Netherlands

8. Department of Internal Medicine and School for Cardiovascular Diseases (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands

9. Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands

10. Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands

11. Department of Epidemiology, ErasmusMC, Rotterdam, The Netherlands

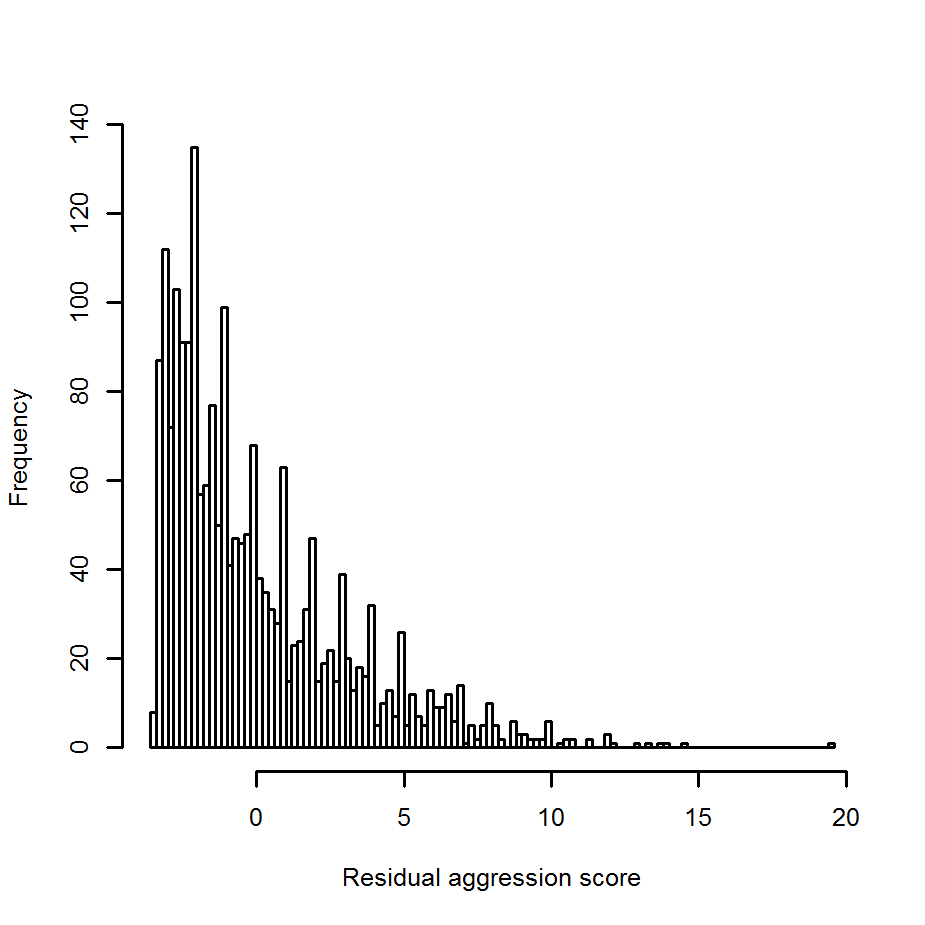
12. Sequence Analysis Support Core, Leiden University Medical Center, Leiden, The Netherlands

13. SURFsara, Amsterdam, the Netherlands

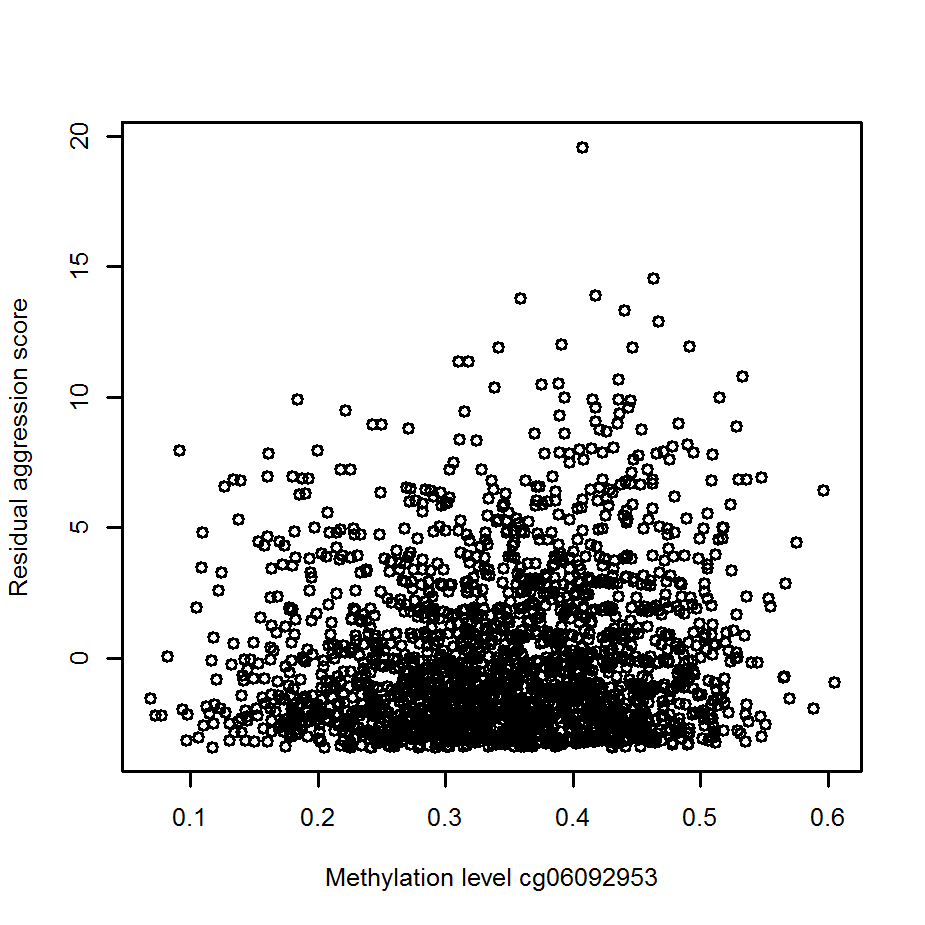
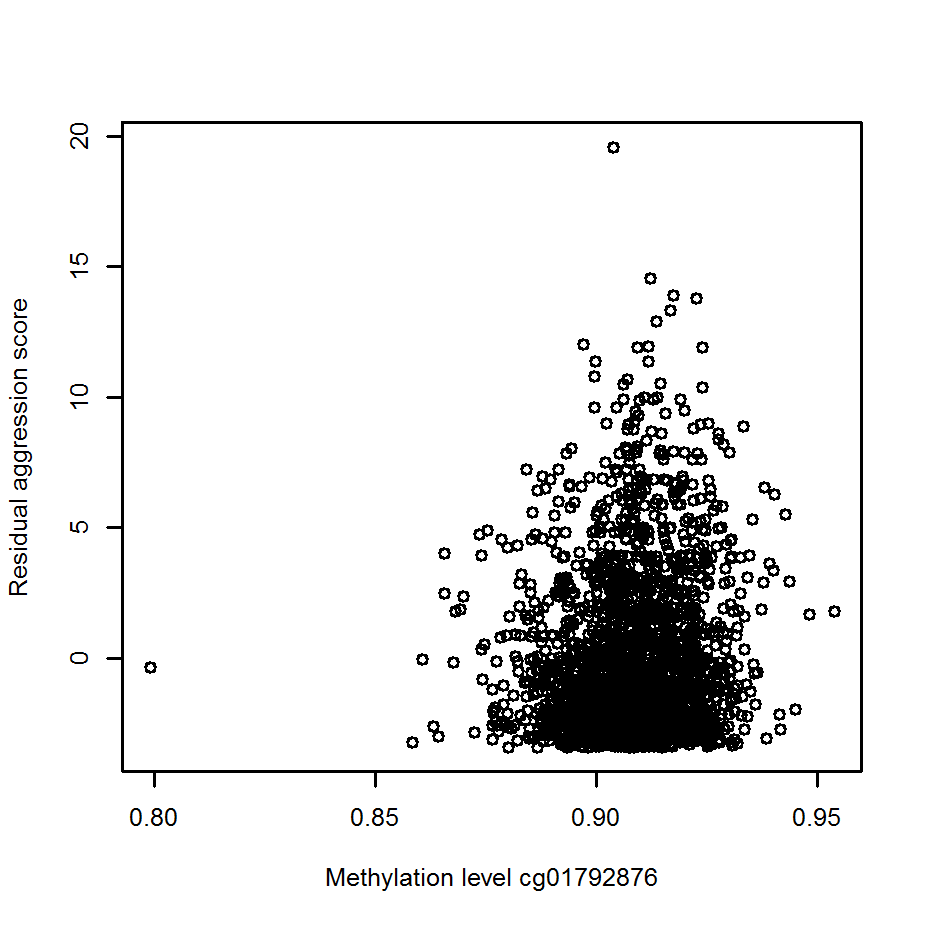
14. Genomics Coordination Center, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

15. Medical Statistics Section, Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands

**Supplementary Figures and Tables**

****

**Supplementary Figure S1:** Distribution of aggression scores in the EWAS.



**Supplementary Figure S2:** Scatterplots for the two top CpGs. Residual aggression scores are plotted against methylation level.

**Supplementary Table S1:** Sex and Age and Effects on Aggression

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | *N* | Intercept | Beta age (standardized beta)A | Robust *SE* age | *P* value age | Beta sex (standardized beta)B | Robust SE sex | *p* value sex |
| Survey 8 | 14,173 | 3.49 | -0.03 (0.01 SD) | 0.0017 | 4.19E-81 | 0.48 (0.15 SD) | 0.05 | 9.60E-19 |
| Survey 10 | 15,535 | 3.26 | -0.03 (0.01 SD) | 0.0017 | 2.37E-72 | 0.46 (0.15 SD) | 0.05 | 2.26E-20 |

Note: Estimates from a generalized estimation equation (GEE) model with ASR aggression score as outcome and age and sex as predictors. AChange in aggression score associated with a one year increase of age. The value between brackets (standardized beta) represents the effect expressed relative to the standard deviation of aggression score in the entire study sample. BDifference in aggression scores between the sexes (women minus men). The value between brackets (standardized beta) represents the effect expressed relative to the standard deviation of aggression score in the entire study sample.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | B | jack SE | jack T | jack P |
| (Intercept) | 1.020733 | 0.012342 | 82.70206 | 0 |
| Mean methylation level | -0.03733 | 0.010074 | -3.70617 | 0.00021 |
| *SD* methylation level | 0.546277 | 0.207655 | 2.6307 | 0.008521 |
| Downstream region | 0.009512 | 0.01956 | 0.486281 | 0.626768 |
| Gene body | 0.01138 | 0.007546 | 1.507976 | 0.131561 |
| Proximal promotor | 0.040094 | 0.008323 | 4.817295 | 1.46E-06 |
| Distal promotor | 0.006778 | 0.0132 | 0.513502 | 0.6076 |
| CpG island (CGI) | 0.004634 | 0.007114 | 0.651411 | 0.514781 |
| CGI shelf | -0.00259 | 0.008718 | -0.29693 | 0.766517 |
| CGI shore | -0.0047 | 0.006976 | -0.67422 | 0.500168 |
| DNase I hypersensitive site | 0.023931 | 0.005261 | 4.548676 | 5.40E-06 |
| Aggression loci | 0.036608 | 0.067437 | 0.542851 | 0.587232 |

**Supplementary Table S2:** Jackknife Estimates for the Regression of EWAS Test Statistics on Genomic Annotation Categories