**Supplementary Methods**

**GWAS of EAAHorvath and EAAHannum**: Blood or saliva samples for GS:SFHS participants were collected, processed, and stored following standard operating procedures; full details of sample collection and DNA extraction are described elsewhere (1). Samples were genotyped as previously described (2). Quality control procedures on the raw genotypes included removal of individuals with a call rate less than 98% and SNPs with a call rate less than 98% or a significant deviation from Hardy-Weinberg equilibrium (P≥1x10–6); full details of QC can be found elsewhere (3). A total of 20,032 individuals, including all participants in the current study (n=5052 for EAAHorvath and n=5047 for EAAHannum), and 604,858 genotyped autosomal SNPs passed all quality control thresholds. To increase the density of variants throughout the genome, genotypes were imputed using the Haplotype Research Consortium reference panel v1.1 (4) via the Sanger Imputation Pipeline (5), as described previously (3). Monogenic or multi-allelic variants, and SNPs with a low imputation quality (INFO<0.4) were removed from the imputed dataset, leaving 24,111,857 variants available for downstream analysis. Given the relatively small sample sizes of the current study, only data from variants with a minor allele frequency greater than 1% were considered, resulting in an imputed dataset with 8,633,288 variants to be used in the genome-wide association analysis.

GWAS of EAAHorvath and EAAHannum were conducted using mixed linear model based association (MLMA) analysis (6), implemented in GCTA (v1.25.) (7), taking into account the sex of the participant, and adjusting for blood cell counts for CD8 T cells, CD4 T cells, natural killer cells, B cells, and granulocytes. As GS:SFHS is a family-based sample, two genomic relationship matrices (GRMs) were used to account for population structure. The first included pairwise relationship coefficients for all individuals. The second had off-diagonal elements of pairs of individuals who had a relationship coefficient < 0.05 set to 0, therefore excluding pairs of individuals that have a most recent common ancestor of approximately four generations distant, assuming no inbreeding (8). Full details of the creation of the GRMs are given elsewhere (9). The two GRMs adequately accounted for population stratification, tested using univariate LD score regression (10), so it was not necessary to include ancestry-informative principal components in the GWAS. Association summary statistics from these GWAS of the two epigenetic age acceleration phenotypes were used for LD score regression, as described in the main text.

**References**

1 Kerr SM, Campbell A, Murphy L, Hayward C, Jackson C, Wain LV et al. Pedigree and genotyping quality analyses of over 10,000 DNA samples from the Generation Scotland: Scottish Family Health Study. BMC Med Genet 2013; **14:** 38.

2 Gunderson KL. Whole-genome genotyping on bead arrays. Methods Mol Biol 2009; **529:** 197-213.

3 Nagy R, Boutin TS, Marten J, Huffman JE, Kerr SM, Campbell A et al. Exploration of haplotype research consortium imputation for genome-wide association studies in 20,032 Generation Scotland participants. Genome Medicine 2017; **9**: 23.

4 McCarthy S, Das S, Kretzschmar W, Durbin R, Abecasis G, Marchini J. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet 2016; **48:** 1279-1283.

5 Sanger Imputation Service. <https://imputation.sanger.ac.uk/>. Accessed 02 Mar 2017.

6 Yang J, Zaitlen NA, Goddard ME, Visscher PM, Price AL. Advantages and pitfalls in the application of mixed-model association methods. Nat Genet 2014; **46**(2)**:** 100-106.

7 Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. Am J Hum Genet 2011; **88**(1)**:** 76-82.

8 Lynch M, Walsh B. Genetics and analysis of quantitative traits. Sinauer: Sunderland, Mass., 1998, xvi, 980 pagespp.

9 Ref Lynsey's stratified depression paper, accepted but not yet published.

10 Bulik-Sullivan BK et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nature Genetics **47**, 291

**Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium**

Naomi R Wray 1, 2

Stephan Ripke 3, 4, 5

Manuel Mattheisen 6, 7, 8, 9

Maciej Trzaskowski\* 1

Enda M Byrne 1

Abdel Abdellaoui 10

Mark J Adams 11

Esben Agerbo 9, 12, 13

Tracy M Air 14

Till F M Andlauer 15, 16

Silviu-Alin Bacanu 17

Marie Bækvad-Hansen 9, 18

Aartjan T F Beekman 19

Tim B Bigdeli 17, 20

Elisabeth B Binder 15, 21

Douglas H R Blackwood 11

Julien Bryois 22

Henriette N Buttenschøn 8, 9, 23

Jonas Bybjerg-Grauholm 9, 18

Na Cai 24, 25

Enrique Castelao 26

Jane Hvarregaard Christensen 7, 8, 9

Toni-Kim Clarke 11

Jonathan R I Coleman 27

Lucía Colodro-Conde 28

Baptiste Couvy-Duchesne 29, 30

Nick Craddock 31

Gregory E Crawford 32, 33

Gail Davies 34

Ian J Deary 34

Franziska Degenhardt 35, 36

Eske M Derks 28

Nese Direk 37, 38

Conor V Dolan 10

Erin C Dunn 39, 40, 41

Thalia C Eley 27

Valentina Escott-Price 42

Farnush Farhadi Hassan Kiadeh 43

Hilary K Finucane 44, 45

Andreas J Forstner 35, 36, 46, 47

Josef Frank 48

Héléna A Gaspar 27

Michael Gill 49

Fernando S Goes 50

Scott D Gordon 51

Jakob Grove 7, 8, 9, 52

Lynsey S Hall 11, 53

Christine Søholm Hansen 9, 18

Thomas F Hansen 54, 55, 56

Stefan Herms 35, 36, 47

Ian B Hickie 57

Per Hoffmann 35, 36, 47

Georg Homuth 58

Carsten Horn 59

Jouke-Jan Hottenga 10

David M Hougaard 9, 18

Marcus Ising 60

Rick Jansen 19, 19

Eric Jorgenson 61

James A Knowles 62

Isaac S Kohane 63, 64, 65

Julia Kraft 4

Warren W. Kretzschmar 66

Jesper Krogh 67

Zoltán Kutalik 68, 69

Yihan Li 66

Penelope A Lind 28

Donald J MacIntyre 70, 71

Dean F MacKinnon 50

Robert M Maier 2

Wolfgang Maier 72

Jonathan Marchini 73

Hamdi Mbarek 10

Patrick McGrath 74

Peter McGuffin 27

Sarah E Medland 28

Divya Mehta 2, 75

Christel M Middeldorp 10, 76, 77

Evelin Mihailov 78

Yuri Milaneschi 19, 19

Lili Milani 78

Francis M Mondimore 50

Grant W Montgomery 1

Sara Mostafavi 79, 80

Niamh Mullins 27

Matthias Nauck 81, 82

Bernard Ng 80

Michel G Nivard 10

Dale R Nyholt 83

Paul F O'Reilly 27

Hogni Oskarsson 84

Michael J Owen 85

Jodie N Painter 28

Carsten Bøcker Pedersen 9, 12, 13

Marianne Giørtz Pedersen 9, 12, 13

Roseann E. Peterson 17, 86

Erik Pettersson 22

Wouter J Peyrot 19

Giorgio Pistis 26

Danielle Posthuma 87, 88

Jorge A Quiroz 89

Per Qvist 7, 8, 9

John P Rice 90

Brien P. Riley 17

Margarita Rivera 27, 91

Saira Saeed Mirza 37

Robert Schoevers 92

Eva C Schulte 93, 94

Ling Shen 61

Jianxin Shi 95

Stanley I Shyn 96

Engilbert Sigurdsson 97

Grant C B Sinnamon 98

Johannes H Smit 19

Daniel J Smith 99

Hreinn Stefansson 100

Stacy Steinberg 100

Fabian Streit 48

Jana Strohmaier 48

Katherine E Tansey 101

Henning Teismann 102

Alexander Teumer 103

Wesley Thompson 9, 55, 104, 105

Pippa A Thomson 106

Thorgeir E Thorgeirsson 100

Matthew Traylor 107

Jens Treutlein 48

Vassily Trubetskoy 4

André G Uitterlinden 108

Daniel Umbricht 109

Sandra Van der Auwera 110

Albert M van Hemert 111

Alexander Viktorin 22

Peter M Visscher 1, 2

Yunpeng Wang 9, 55, 105

Bradley T. Webb 112

Shantel Marie Weinsheimer 9, 55

Jürgen Wellmann 102

Gonneke Willemsen 10

Stephanie H Witt 48

Yang Wu 1

Hualin S Xi 113

Jian Yang 2, 114

Futao Zhang 1

Volker Arolt 115

Bernhard T Baune 14

Klaus Berger 102

Dorret I Boomsma 10

Sven Cichon 35, 47, 116, 117

Udo Dannlowski 115

EJC de Geus 10, 118

J Raymond DePaulo 50

Enrico Domenici 119

Katharina Domschke 120

Tõnu Esko 5, 78

Hans J Grabe 110

Steven P Hamilton 121

Caroline Hayward 122

Andrew C Heath 90

Kenneth S Kendler 17

Stefan Kloiber 60, 123, 124

Glyn Lewis 125

Qingqin S Li 126

Susanne Lucae 60

Pamela AF Madden 90

Patrik K Magnusson 22

Nicholas G Martin 51

Andrew M McIntosh 11, 34

Andres Metspalu 78, 127

Ole Mors 9, 128

Preben Bo Mortensen 8, 9, 12, 13

Bertram Müller-Myhsok 15, 16, 129

Merete Nordentoft 9, 130

Markus M Nöthen 35, 36

Michael C O'Donovan 85

Sara A Paciga 131

Nancy L Pedersen 22

Brenda WJH Penninx 19

Roy H Perlis 39, 132

David J Porteous 106

James B Potash 133

Martin Preisig 26

Marcella Rietschel 48

Catherine Schaefer 61

Thomas G Schulze 48, 94, 134, 135, 136

Jordan W Smoller 39, 40, 41

Kari Stefansson 100, 137

Henning Tiemeier 37, 138, 139

Rudolf Uher 140

Henry Völzke 103

Myrna M Weissman 74, 141

Thomas Werge 9, 55, 142

Cathryn M Lewis 27, 143

Douglas F Levinson 144

Gerome Breen 27, 145

Anders D Børglum 7, 8, 9

Patrick F Sullivan 22, 146, 147,

1, Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU

2, Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU

3, Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, US

4, Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, DE

5, Medical and Population Genetics, Broad Institute, Cambridge, MA, US

6, Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, SE

7, Department of Biomedicine, Aarhus University, Aarhus, DK

8, iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK

9, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research,, DK

10, Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL

11, Division of Psychiatry, University of Edinburgh, Edinburgh, GB

12, Centre for Integrated Register-based Research, Aarhus University, Aarhus, DK

13, National Centre for Register-Based Research, Aarhus University, Aarhus, DK

14, Discipline of Psychiatry, University of Adelaide, Adelaide, SA, AU

15, Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE

16, Munich Cluster for Systems Neurology (SyNergy), Munich, DE

17, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US

18, Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK

19, Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, NL

20, Virginia Institute for Psychiatric and Behavior Genetics, Richmond, VA, US

21, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, US

22, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE

23, Department of Clinical Medicine, Translational Neuropsychiatry Unit, Aarhus University, Aarhus, DK

24, Human Genetics, Wellcome Trust Sanger Institute, Cambridge, GB

25, Statistical genomics and systems genetics, European Bioinformatics Institute (EMBL-EBI), Cambridge, GB

26, Department of Psychiatry, University Hospital of Lausanne, Prilly, Vaud, CH

27, MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB

28, Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Herston, QLD, AU

29, Centre for Advanced Imaging, The University of Queensland, Saint Lucia, QLD, AU

30, Queensland Brain Institute, The University of Queensland, Saint Lucia, QLD, AU

31, Psychological Medicine, Cardiff University, Cardiff, GB

32, Center for Genomic and Computational Biology, Duke University, Durham, NC, US

33, Department of Pediatrics, Division of Medical Genetics, Duke University, Durham, NC, US

34, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB

35, Institute of Human Genetics, University of Bonn, Bonn, DE

36, Life&Brain Center, Department of Genomics, University of Bonn, Bonn, DE

37, Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, NL

38, Psychiatry, Dokuz Eylul University School Of Medicine, Izmir, TR

39, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, US

40, Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, US

41, Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, US

42, Neuroscience and Mental Health, Cardiff University, Cardiff, GB

43, Bioinformatics, University of British Columbia, Vancouver, BC, CA

44, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, US

45, Department of Mathematics, Massachusetts Institute of Technology, Cambridge, MA, US

46, Department of Psychiatry (UPK), University of Basel, Basel, CH

47, Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, CH

48, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health,  Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE

49, Department of Psychiatry, Trinity College Dublin, Dublin, IE

50, Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US

51, Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, AU

52, Bioinformatics Research Centre, Aarhus University, Aarhus, DK

53, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, GB

54, Danish Headache Centre, Department of Neurology, Rigshospitalet, Glostrup, DK

55, Institute of Biological Psychiatry, Mental Health Center Sct. Hans, Mental Health Services Capital Region of Denmark, Copenhagen, DK

56, iPSYCH, The Lundbeck Foundation Initiative for Psychiatric Research, Copenhagen, DK

57, Brain and Mind Centre, University of Sydney, Sydney, NSW, AU

58, Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Mecklenburg-Vorpommern, DE

59, Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH

60, Max Planck Institute of Psychiatry, Munich, DE

61, Division of Research, Kaiser Permanente Northern California, Oakland, CA, US

62, Psychiatry & The Behavioral Sciences, University of Southern California, Los Angeles, CA, US

63, Department of Biomedical Informatics, Harvard Medical School, Boston, MA, US

64, Department of Medicine, Brigham and Women's Hospital, Boston, MA, US

65, Informatics Program, Boston Children's Hospital, Boston, MA, US

66, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, GB

67, Department of Endocrinology at Herlev University Hospital, University of Copenhagen, Copenhagen, DK

68, Institute of Social and Preventive Medicine (IUMSP), University Hospital of Lausanne, Lausanne, VD, CH

69, Swiss Institute of Bioinformatics, Lausanne, VD, CH

70, Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, GB

71, Mental Health, NHS 24, Glasgow, GB

72, Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, DE

73, Statistics, University of Oxford, Oxford, GB

74, Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, US

75, School of Psychology and Counseling, Queensland University of Technology, Brisbane, QLD, AU

76, Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, South Brisbane, QLD, AU

77, Child Health Research Centre, University of Queensland, Brisbane, QLD, AU

78, Estonian Genome Center, University of Tartu, Tartu, EE

79, Medical Genetics, University of British Columbia, Vancouver, BC, CA

80, Statistics, University of British Columbia, Vancouver, BC, CA

81, DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE

82, Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE

83, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, AU

84, Humus, Reykjavik, IS

85, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, GB

86, Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, US

87, Clinical Genetics, Vrije Universiteit Medical Center, Amsterdam, NL

88, Complex Trait Genetics, Vrije Universiteit Amsterdam, Amsterdam, NL

89, Solid Biosciences, Boston, MA, US

90, Department of Psychiatry, Washington University in Saint Louis School of Medicine, Saint Louis, MO, US

91, Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, ES

92, Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, NL

93, Department of Psychiatry and Psychotherapy, Medical Center of the University of Munich, Campus Innenstadt, Munich, DE

94, Institute of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich, Campus Innenstadt, Munich, DE

95, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, US

96, Behavioral Health Services, Kaiser Permanente Washington, Seattle, WA, US

97, Faculty of Medicine, Department of Psychiatry, University of Iceland, Reykjavik, IS

98, School of Medicine and Dentistry, James Cook University, Townsville, QLD, AU

99, Institute of Health and Wellbeing, University of Glasgow, Glasgow, GB

100, deCODE Genetics / Amgen, Reykjavik, IS

101, College of Biomedical and Life Sciences, Cardiff University, Cardiff, GB

102, Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, DE

103, Institute for Community Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE

104, Department of Psychiatry, University of California, San Diego, San Diego, CA, US

105, KG Jebsen Centre for Psychosis Research, Norway Division of Mental Health and Addiction, Oslo University Hospital, Oslo, NO

106, Medical Genetics Section, CGEM, IGMM, University of Edinburgh, Edinburgh, GB

107, Clinical Neurosciences, University of Cambridge, Cambridge, GB

108, Internal Medicine, Erasmus MC, Rotterdam, Zuid-Holland, NL

109, Roche Pharmaceutical Research and Early Development, Neuroscience, Ophthalmology and Rare Diseases Discovery & Translational Medicine Area, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH

110, Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE

111, Department of Psychiatry, Leiden University Medical Center, Leiden, NL

112, Virginia Institute of Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, US

113, Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, US

114, Institute for Molecular Bioscience; Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU

115, Department of Psychiatry, University of Münster, Münster, Nordrhein-Westfalen, DE

116, Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Basel, CH

117, Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, DE

118, Amsterdam Public Health Institute, Vrije Universiteit Medical Center, Amsterdam, NL

119, Centre for Integrative Biology, Università degli Studi di Trento, Trento, Trentino-Alto Adige, IT

120, Department of Psychiatry and Psychotherapy, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, DE

121, Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, US

122, Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, GB

123, Department of Psychiatry, University of Toronto, Toronto, ON, CA

124, Centre for Addiction and Mental Health, Toronto, ON, CA

125, Division of Psychiatry, University College London, London, GB

126, Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, US

127, Institute of Molecular and Cell Biology, University of Tartu, Tartu, EE

128, Psychosis Research Unit, Aarhus University Hospital, Risskov, Aarhus, DK

129, University of Liverpool, Liverpool, GB

130, Mental Health Center Copenhagen, Copenhagen Universtity Hospital, Copenhagen, DK

131, Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, US

132, Psychiatry, Harvard Medical School, Boston, MA, US

133, Psychiatry, University of Iowa, Iowa City, IA, US

134, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US

135, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Goettingen, Niedersachsen, DE

136, Human Genetics Branch, NIMH Division of Intramural Research Programs, Bethesda, MD, US

137, Faculty of Medicine, University of Iceland, Reykjavik, IS

138, Child and Adolescent Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL

139, Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL

140, Psychiatry, Dalhousie University, Halifax, NS, CA

141, Division of Epidemiology, New York State Psychiatric Institute, New York, NY, US

142, Department of Clinical Medicine, University of Copenhagen, Copenhagen, DK

143, Department of Medical & Molecular Genetics, King's College London, London, GB

144, Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA, US

145, NIHR BRC for Mental Health, King's College London, London, GB

146, Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, US

147, Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, US

**Supplementary Table 1** Models including [age\*MDD] and, or [sex\*MDD] interactions

|  |  |
| --- | --- |
|  | **MDD** |
| **EAA Horvath clock (as in main analyses)** | **β** | **P value** |
| Controlling for relatedness, sex | 0.1103  | **8.41x10-4** |
| Controlling for above plus cell counts and batch | 0.0804 | **0.012** |
| Controlling for above plus smoking | 0.0811 | **0.013** |
| Controlling for above plus drinking | 0.0765 | **0.020** |
| Controlling for above plus BMI | 0.0647 | **0.049** |
|  | **MDD** | **MDD\*age** |
| **EAA Horvath clock** | **β** | **P value** | **β** | **P value** |
| Controlling for relatedness, sex, **& MDD\*age** | 0.1098 | **8.36x10-4** | -0.0626 | 0.076 |
| Controlling for above plus cell counts and batch | 0.0797 | **0.012** | -0.0667 | 0.052 |
| Controlling for above plus smoking | 0.0809 | **0.013** | -0.0724 | **0.038** |
| Controlling for above plus drinking | 0.0763 | **0.020** | -0.0906 | **0.010** |
| Controlling for above plus BMI | 0.0644 | 0.051 | -0.0949 | **0.007** |
|  | **MDD** | **MDD\*sex** |
| **EAA Horvath clock** | **β** | **P value** | **β** | **P value** |
| Controlling for relatedness, sex, **&** **MDD\*sex** | 0.1174 | **8.42x10-4** | -0.0229 | 0.743 |
| Controlling for above plus cell counts and batch | 0.0915 | **0.012** | -0.0358 | 0.597 |
| Controlling for above plus smoking | 0.0862 | **0.013** | -0.0167 | 0.809 |
| Controlling for above plus drinking | 0.0803 | **0.020** | -0.0122 | 0.860 |
| Controlling for above plus BMI | 0.0628 | **0.048** | 0.0062 | 0.928 |
|  | **MDD** | **MDD\*age/MDD\*sex** |
| **EAA Horvath clock** | **β** | **P value** | **β** | **P value** |
| Controlling for relatedness, sex, **&** **MDD\*age, MDD\*sex** | 0.1159 | **8.37x10-4** | -0.0624/ 0.0197 | 0.078/0.778 |
| Controlling for above plus cell counts and batch | 0.0893 | **0.012** | -0.0662/-0.0308 | 0.054/0.649 |
| Controlling for above plus smoking | 0.080 | **0.013** | -0.0723/-0.0103 | **0.038**/0.882 |
| Controlling for above plus drinking | 0.0776 | **0.020** | -0.0906/-0.0044 | **0.010**/0.950 |
| Controlling for above plus BMI | 0.0593 | 0.051 | -0.0952/0.0163 | **0.007**/0.813 |

**Supplementary Table 2** Results for Sobel mediation test

|  |  |  |
| --- | --- | --- |
|  | **B** | **P value** |
| **MDD status as dependent variable (DV), BMI (mediator)** |
| **MDD status (DV), EAA Hannum (IV):** n/s |
| **MDD status (DV), EAA Horvath (IV)** |
| Partial effect IV on M (a path) | 0.0878 | **3.07x10****-4** |
| Direct effect M on DV (b path) | 0.0315 | **0.004** |
| Direct effect IV on DV (c path) | 0.0219 | **0.046** |
| Total effect IV on DV (c’ path) | 0.0249 | **0.023** |
| **Indirect effect (ab path)** | **0.0028** | **0.025** |
| **Proportion mediated** | **12.79%** | **-** |
| **MDD status as dependent variable (DV), smoking status (mediator)** |
| **MDD status (DV), EAA Horvath (IV)** |
| Partial effect IV on M (a path) | -0.0581 | **0.032** |
| Direct effect M on DV (b path) | -0.0150 | 0.130 |
| Direct effect IV on DV (c path) | 0.0219 | **0.046** |
| Total effect IV on DV (c’ path) | 0.0229 | **0.036** |
| **Indirect effect (ab path)** | 0.0009 | 0.216 |
| **Proportion mediated** | 4.11% | **-** |
| **MDD status as dependent variable (DV), drinking status (mediator)** |
| **MDD status (DV), EAA Horvath (IV)** |
| Partial effect IV on M (a path) | <0.0001 | 0.080 |
| Direct effect M on DV (b path) | -0.0148 | 0.129 |
| Direct effect IV on DV (c path) | 0.0215 | **0.048** |
| Total effect IV on DV (c’ path) | 0.0215 | **0.048** |
| **Indirect effect (ab path)** | <0.0001 | 0.251 |
| **Proportion mediated** | <0.01% | **-** |

DV = Dependent Variable, IV = Independent Variable, EAA = Epigenetic Age Acceleration. All models controlling for sex, relatedness, processing batch, cell counts (& smoking/drinking/BMI when not included as mediator).

**Supplementary Figure 1:** Correlation between epigenetic age and chronological age for Hannum and Horvath clocks

