**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.

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**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

