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Meta-analyses of epigenetic age acceleration and GrimAge components of schizophrenia or first-episode psychosis

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Schizophrenia is a common chronic psychiatric disorder that causes age-related dysfunction. The life expectancy in patients with schizophrenia is ≥10 years shorter than that in the general population because of the higher risk of other diseases, such as cardiovascular diseases. Aging studies based on DNA methylation status have received considerable attention. Several epigenetic age accelerations and predicted values of aging-related proteins (GrimAge and GrimAge2 components) have been analyzed in multiple diseases. However, no studies have investigated up to GrimAge and GrimAge2 components between patients with schizophrenia and controls. Therefore, we aimed to conduct multiple regression analyses to investigate the association between schizophrenia and epigenetic age accelerations and GrimAge and GrimAge2 components in seven cohorts. Furthermore, we included patients with first-episode psychosis whose illness duration was often shorter than schizophrenia in our analysis. We integrated these results with meta-analyses, noting the acceleration of GrimAge, GrimAge2, and DunedinPACE, and increase in adrenomedullin, beta-2 microglobulin, cystatin C, and plasminogen activation inhibitor-1 levels, in patients with schizophrenia or first-episode psychosis. These results corroborated the finding that patients with schizophrenia had an increased risk of diabetes, cardiovascular disease, and cognitive dysfunction from a biological perspective. Patients with schizophrenia and first-episode psychosis showed differences in the results when compared with controls. Such analyses may lead to the development of novel therapeutic targets to patients with schizophrenia or relevant diseases from the perspective of aging in the future.

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INTRODUCTION

Schizophrenia is a chronic psychiatric disorder with an incidence rate of ~1%[1]. Some changes associated with aging of the brain are observed in patients with schizophrenia, such as widespread cerebral cortical atrophy[2], dendritic spine loss[3,4], and cognitive dysfunction[5]. The life expectancy in patients with schizophrenia is ≥10 years shorter than that in the general population[6]. The mortality rate in patients with schizophrenia is high not only because of suicide and accidental deaths but also owing to increased risk of cardiovascular and respiratory diseases[7]. Moreover, smoking[8], diabetes[9], obesity[10], and hyperlipidemia[11] are more common in patients with schizophrenia than in the general population. Accelerated aging in patients with schizophrenia has been proposed as a possible explanation for these findings[12]. In addition, patients diagnosed with first-episode psychosis experience cognitive dysfunction as well as those with schizophrenia because psychotic symptoms are similar, although the duration of first-episode psychosis is shorter and its prognosis is relatively better, than those of schizophrenia[13,14].

Recently, the finding that epigenetic changes in DNA methylation (DNAm) affect biological aging has received considerable attention[15,16]. Multiple measurements of biological aging, such as several epigenetic clocks, have been established based on the genome-wide DNAm status[17–22]. The estimated epigenetic age acceleration has been associated with psychiatric disorders[23–28], neurodegenerative disorders[29,30], and all-cause mortality[31].

Various epigenetic clocks have been developed using elastic net regression. Elastic net regression is a machine learning method that uses penalization techniques to set the coefficients of unimportant variables to zero, preventing overfitting. These select hundreds to thousands of important cytosine-phosphate-guanine (CpG) sites out of about 900,000 sites and calculate biological aging from these methylation rates and individual coefficients. In elastic net regression when epigenetic clocks creation, cross-validation is used to determine the λ value for parameter adjustment, with the R package glmnet[32]. First, Horvath developed HorvathAge using 353 CpG sites based on comprehensive DNAm status in multiple tissues (such as peripheral blood, umbilical cord blood, buccal mucosa, frontal lobe, pons, large intestine, heart, kidney, and liver)[17]. Subsequently, HannumAge and SkinBloodAge were developed using 71 CpG sites from blood samples[18], and 391 CpG sites from fibroblast, keratinocyte, buccal mucosal cell, endothelial cell, lymphoblast, skin cells, blood, and saliva samples[19], respectively. These three epigenetic clocks were established as formulas for predicting actual age. Conversely, PhenoAge was established by defining the mortality rate owing to heart diseases, malignant tumors, chronic lower respiratory tract diseases, cerebrovascular diseases, Alzheimer's disease, diabetes, nephritis, and nephrotic syndromes as "mortality rate due to aging", and regressing that "mortality rate due to aging" on DNAm status from blood samples. As the results, 513 CpG sites were selected and PhenoAge uses the DNAm status of these sites[20].

Lu et al. developed GrimAge with 1030 CpG sites from blood samples using a composite biomarker based on chronological age, sex, seven DNAm-based prediction levels of aging-related plasma proteins (adrenomedullin [ADM], beta-2 microglobulin [B2M], cystatin C, growth differentiation factor-15 [GDF15], leptin, plasminogen activation inhibitor-1 [PAI1], and tissue inhibitor of metalloproteinases-1 [TIMP1]), and DNAm-based smoking pack-

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years (DNAmPACKYRS)[21]. To establish GrimAge, first, DNAm-based prediction formulas of the levels of 88 plasma proteins related to aging were developed, then proteins with correlation coefficients of >0.35 between predicted and actual values in another independent cohort were selected (12 proteins). Furthermore, using elastic net regression of the time-to-death (due to all causes), seven plasma proteins were selected, and the formula was developed to predict life expectancy based on DNAm-based predicted values of the levels of these seven plasma proteins, DNAmPACKYRS, age and sex. Using these, an algorithm was established to predict life expectancy from 1030 CpG sites in two-stage approach as GrimAge. GrimAge2, which was also developed by Lu et al., predicts life expectancy by adding DNAm-based predicted values of C reactive protein (CRP) and hemoglobin A1c (HbA1c) to the explanatory variables used in GrimAge. GrimAge2 showed slightly higher accuracies in predicting the aging reflecting the period until death, association with coronary heart diseases, and association with lung function than those of GrimAge. GrimAge2 also showed higher prediction accuracy within each of the multiple ethnic groups (White, African American, and Hispanic verified using ancestry-specific single nucleotide polymorphism [SNP] markers)[22]. The DNAm-based predicted plasma protein levels used for calculating GrimAge and GrimAge2 are termed "GrimAge components" and "GrimAge2 components", respectively. Furthermore, although these are still not used as biomarkers in actual psychiatric clinical practice, proteins belonging to GrimAge components are also highly associated with the nervous system[33–36]. In research on psychiatry and neurology, examining the disease-specific changes in these individual components is worthwhile. We previously reported an elevated predictive value of cystatin C based on DNAm status in patients with depression[28]. Although cystatin C is not yet being used in practice as a clinical marker for psychiatric diseases, an increasing number of reports is linking cystatin C to major depressive disorder, depressive states, and suicidal thoughts[37].

Moreover, DNAm-based telomere length (DNAmTL) predicts telomere length, which shortens with aging and cell replication[38,39]. DunedinPACE is a measure used to quantify biological aging acceleration based on the prediction of physical and cognitive function biomarkers[40]. Each measure has different points regarding the type of epigenetic data and tissue sample on which they are trained and captures certain aspects of biological aging. They have been successfully applied to the study of various psychiatric disorders[41].

In our previous study, we showed decreased AgeAccelHannum adjusted with cell compositions in Japanese patients with schizophrenia under long-term or repeated hospitalizations at Kobe University[27]. Although multiple studies have similarly examined schizophrenia and epigenetic age, few have validated epigenetic clocks relatively recently developed. Caspi et al. investigated variable indices of epigenetic aging acceleration, including newly developed indices, and showed increase in DunedinPACE in patients with schizophrenia[42]. In this study, we aimed to examine the differences in aging between patients with schizophrenia or first-episode psychosis and healthy controls using multiple indices, including multiple epigenetic clocks and GrimAge and GrimAge2 components as aging-related proteins.

RESULTS

Results for each cohort

Regarding demographic data, several cohorts showed significant differences in sex and/or age between the controls and patients (schizophrenia or first-episode psychosis) (Supplementary Table 1). We conducted regression analyses using two models: the first regression model includes age, sex, and DNAmPACKYRS as confounding factors, and the second regression model added DNAm-based white blood cell compositions in confounding factors. The results of the multiple regression analyses of the first regression model for the eight epigenetic age acceleration, eight GrimAge components, and six GrimAge2 components are shown in Supplementary Tables 2–8 for Japan, GSE41169, GSE80417, GSE84727, GSE147221, GSE152026, and GSE152027 cohorts, respectively. Violin plots for each epigenetic age acceleration in each group are shown in Supplementary Figs. 1–7 for Japan, GSE41169, GSE80417, GSE84727, GSE147221, GSE152026, and GSE152027 cohorts, respectively. Violin plots for each GrimAge component for each group are shown in Supplementary Figs. 8–14 for Japan, GSE41169, GSE80417, GSE84727, GSE147221, GSE152026, and GSE152027 cohorts, respectively. Violin plots for each GrimAge2 component in each group are shown in Supplementary Figs. 15–21 for the Japanese, GSE41169, GSE80417, GSE84727, GSE147221, GSE152026, and GSE152027 cohorts, respectively. Furthermore, the results of Kolmogorov–Smirnov tests and F tests for each item are listed in Supplementary Table 9. The results of the examination of multicollinearity for the explanatory variables of the first and second regression models are shown in Supplementary Table 10.

Meta-analyses with seven cohorts (including first-episode psychosis) in the first regression model

The results of the meta-analyses integrating of the results of regression analyses using the first model for each item in the seven cohorts are shown in Table 1. Among epigenetic age accelerations, AgeAccelPheno ($p = 0.0302$), AgeAccelGrim ($p = 2.59 \times 10^{-3}$), AgeAccelGrim2 ($p = 1.06 \times 10^{-3}$), age-adjusted estimate of DNAm-based TL (DNAmTLAdjAge) ($p = 7.83 \times 10^{-3}$), and DunedinPACE ($p = 3.41 \times 10^{-3}$) showed significant differences between patients and controls. Among GrimAge components, DNAmADM ($p = 3.83 \times 10^{-3}$), DNAmB2M ($p = 0.0161$), DNAmCystatinC ($p = 3.04 \times 10^{-5}$), DNAmPAI1 ($p = 0.0439$), and DNAmPACKYRS ($p = 1.43 \times 10^{-20}$) showed significant differences between patients and controls. Among GrimAge2 components, DNAmadm ($p = 2.04 \times 10^{-3}$), DNAmCystatin_C ($p = 1.23 \times 10^{-3}$), and DNAmpai_1 ($p = 0.0441$) showed significant differences between patients and controls. Figure 1 displays the forest plots of AgeAccelPheno, AgeAccelGrim, AgeAccelGrim2, DNAmTLAdjAge, and DunedinPACE out of the epigenetic age acceleration. Figure 2 displays the forest plots of DNAmADM, DNAmB2M, DNAmCystatin C, and DNAmPAI1 out of the GrimAge components.

Meta-analyses with five cohorts (excluding first-episode psychosis) in the first regression model

Next, we integrated the five cohorts comparing patients with schizophrenia, excluding those with first-episode psychosis, with controls and performed meta-analyses (Table 2). Among epigenetic age accelerations, AgeAccelPheno ($p = 0.0277$), AgeAccelGrim ($p = 6.23 \times 10^{-15}$), AgeAccelGrim2 ($p = 1.455 \times 10^{-8}$), DNAmTLAdjAge ($p = 4.33 \times 10^{-3}$), and DunedinPACE ($p = 7.85 \times 10^{-5}$) showed significant differences between patients and controls. Among the GrimAge components, DNAmADM ($p = 5.37 \times 10^{-8}$), DNAmB2M ($p = 0.0128$), DNAmCystatinC ($p = 1.01 \times 10^{-8}$), DNAmPAI1 ($p = 3.62 \times 10^{-7}$), and DNAmPACKYRS ($p = 2.95 \times 10^{-41}$) showed significant differences between patients and controls. Among the GrimAge2 components, DNAmadm ($p = 1.14 \times 10^{-7}$), DNAmCystatin_C ($p = 2.74 \times 10^{-7}$), and DNAmpai_1 ($p = 3.75 \times 10^{-7}$) showed significant differences between patients and controls. Supplementary Fig. 22 displays the forest plots of AgeAccelPheno, AgeAccelGrim, AgeAccelGrim2, DNAmTLAdjAge, and DunedinPACE. Supplementary Fig. 23 displays the forest plots of DNAmADM, DNAmB2M, DNAmCystatin C, and DNAmPAI1.

Table 1. Results of meta-analyses of seven cohorts comparing patients with schizophrenia or first-episode psychosis and controls in the first regression model.

	Effect size (95% CI)	Standard error	*z*-value	*p*-value	I^2 (%)
Epigenetic age acceleration					
AgeAccelHorvath	0.01436 (−0.04974–0.07846)	0.03271	0.4390	0.6607	59.84771
AgeAccelHannum	0.06565 (0.0071–0.12419)	0.02987	2.1978	***0.02796***	54.07542
AgeAccelSkinBlood	0.00506 (−0.07359–0.0837)	0.04013	0.1261	0.8997	72.98467
AgeAccelPheno	0.04658 (0.00447–0.0887)	0.02149	2.1681	***0.03015***	18.28734
AgeAccelGrim	0.05105 (0.01783–0.08426)	0.01695	3.0123	$\boldsymbol{2.593 \times 10^{-3}}$	73.93120
AgeAccelGrim2	0.06189 (0.02485–0.09893)	0.01890	3.2752	$\boldsymbol{1.056 \times 10^{-3}}$	70.99716
DNAmTLAdjAge	0.0476 (0.01251–0.08268)	0.01790	2.6592	$\boldsymbol{7.834 \times 10^{-3}}$	0.28555
DunedinPACE	0.11032 (0.03647–0.18418)	0.03768	2.9278	$\boldsymbol{3.413 \times 10^{-3}}$	81.76752
GrimAge component					
DNAmADM	0.04583 (0.01477–0.07689)	0.01585	2.8918	$\boldsymbol{3.831 \times 10^{-3}}$	50.64403
DNAmB2M	0.01954 (0.00363–0.03544)	0.00811	2.4079	***0.01605***	1.03658
DNAmCystatinC	0.04409 (0.02337–0.06482)	0.01057	4.1701	$\boldsymbol{3.044 \times 10^{-5}}$	36.13580
DNAmGDF15	0.01334 (−0.0074–0.03408)	0.01058	1.2603	0.2076	0.00000
DNAmLeptin	0.01771 (−0.01031–0.04573)	0.01429	1.2390	0.2153	20.33215
DNAmPAI1	0.07005 (0.00191–0.13818)	0.03476	2.0150	***0.04391***	70.90783
DNAmTIMP1	0.02497 (−0.00107–0.05101)	0.01329	1.8796	0.06016	82.00243
DNAmPACKYRS	0.38428 (0.30328–0.46529)	0.04133	9.2978	$\boldsymbol{1.434 \times 10^{-20}}$	84.76522
GrimAge2 component					
DNAmadm	0.05165 (0.01883–0.08447)	0.01675	3.0847	$\boldsymbol{2.037 \times 10^{-3}}$	48.10259
DNAmCystatin_C	0.05085 (0.02001–0.08168)	0.01573	3.2323	$\boldsymbol{1.228 \times 10^{-3}}$	54.99437
DNAmGDF_15	0.01927 (−0.00789–0.04643)	0.01386	1.3906	0.1643	21.94192
DNAmleptin	0.01907 (−0.00924–0.04738)	0.01444	1.3201	0.1868	21.61222
DNAmpai_1	0.06994 (0.00185–0.13804)	0.03474	2.0131	***0.04411***	70.87446
DNAmTIMP_1	0.0263 (−0.01644–0.06904)	0.02181	1.2059	0.2278	86.32211

All values were calculated by meta-analyses using a random-effects model with standardized regression coefficients and standard errors for phenotypes in each cohort using the R package metafor. In these regression analyses, the first regression model was used.
The first regression model: Each item (Age acceleration, GrimAge component, or GrimAge2 component) ~ Phenotype (controls or patients) + Age + Sex + DNAmPACKYRS.
I^2 values were used to evaluate heterogeneity (0–40%, might not be important; 30–60%, may present moderate heterogeneity; 50–90%, may present substantial heterogeneity; 75–100%, considerable heterogeneity).
ADM adrenomedullin, *adm adrenomedullin*, *B2M* beta-2 microglobulin, *CI* confidence interval, *DNAm* DNA methylation, *DNAmPACKYRS* DNA methylation-based smoking pack-years, *DNAmTLadjAge* age-adjusted estimate of DNA methylation-based telomere length, *GDF15* growth differentiation factor-15, *GDF_15* growth differentiation factor-15, *PAI1* plasminogen activation inhibitor-1, *pai_1* plasminogen activation inhibitor-1, *TIMP-1* tissue inhibitor of metalloproteinases-1, *TIMP_1* tissue inhibitor of metalloproteinases-1.
$p < 0.05$ are shown in bold and italic.

Meta-analyses with two cohorts (only first-episode psychosis) in the first regression model

Furthermore, we integrated the two cohorts comparing individuals with first-episode psychosis with controls, and performed a meta-analysis (Supplementary Table 11). In this analysis, only AgeAccelHannum ($p = 0.038$) and DNAmPACKYRS ($p = 5.30 \times 10^{-28}$) showed significant differences between patients and controls.

Meta-analyses in the second regression model

The results of meta-analyses in the second regression model integrating seven cohorts (including first-episode psychosis) or integrating five cohorts (excluding first-episode psychosis) are listed in Supplementary Tables 12 and 13, respectively. In the meta-analyses of seven cohorts, AgeAccelGrim2, DNAmTLAdgAge, DunedinPACE, DNAmCystatinC, DNAmPACKYRS, and DNAmCystatin_C showed significant differences between patients and controls (Supplementary Table 12). In the meta-analyses of five cohorts, AgeAccelGrim, AgeAccelGrim2, DNAmTLAdgAge, DunedinPACE, DNAmCystatinC, DNAmLeptin, DNAmPAI1, DNAmTIMP1, DNAmPACKYRS, DNAmCystatin_C, DNAmleptin, and DNAmpai_1 showed significant differences between patients and controls (Supplementary Table 13). We created forest plots as we did for the first regression model. For the meta-analyses integrating seven cohorts (including first-episode psychosis), forest plots of the epigenetic age acceleration are displayed in Supplementary Fig. 24 and GrimAge components in Supplementary Fig. 25. For the meta-analyses integrating five cohorts (excluding first-episode psychosis), forest plots of the epigenetic age acceleration are displayed in Supplementary Fig. 26 and GrimAge components in Supplementary Fig. 27.

Meta-analyses integrating results of each subgroup regression analyses in the first regression model

We next conducted subgroup analyses using the first regression model and conducted meta-analyses using the first regression model, against only males, only females, and participants under 40 years old in each cohort.

The results of meta-analyses for only males integrating seven cohorts (including first-episode psychosis) or integrating five

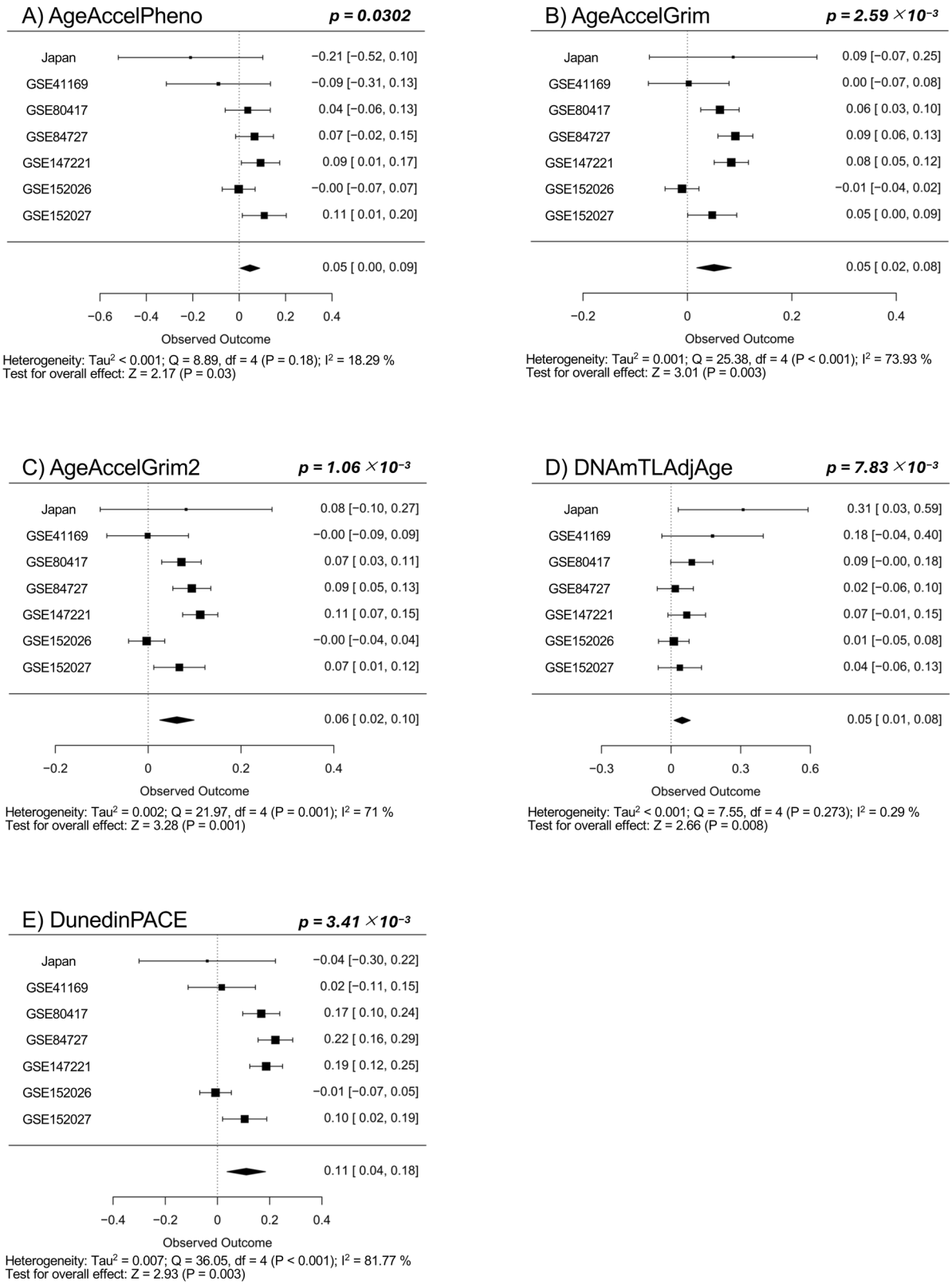

Fig. 1 The forest plots on the age acceleration of note from meta-analyses for seven cohorts comparing patients with schizophrenia or first-episode psychosis, with controls, in the first regression model. A AgeAccelPheno, **B** AgeAccelGrim, **C** AgeAccelGrim2, **D** DNAmTLAdjAge, and (**E**) DunedinPACE. Figure creation and statistical calculations are performed using the R package metafor. DNAm DNA methylation, DNAmTLAdjAge age-adjusted estimate of DNA methylation-based telomere length.

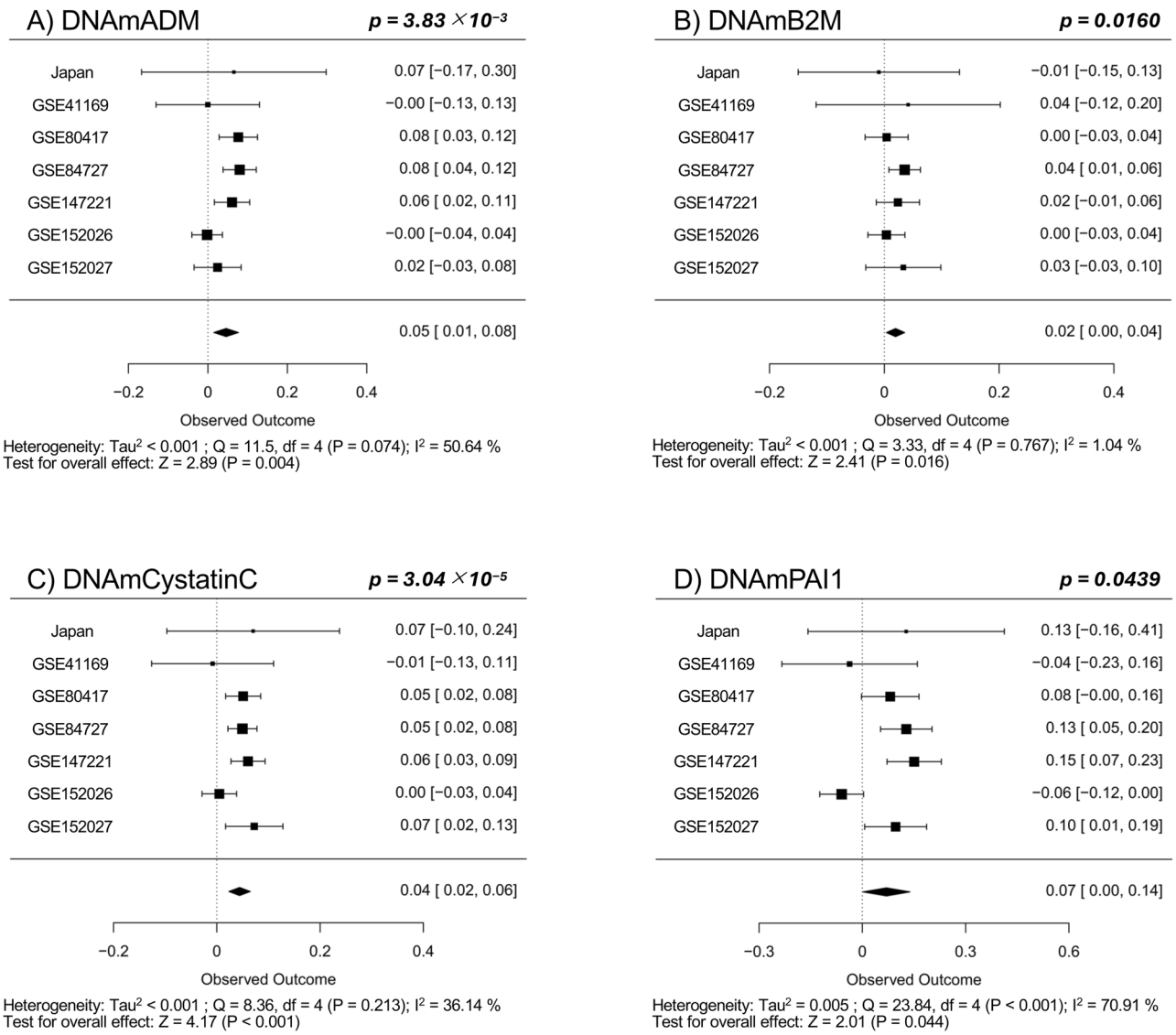

Fig. 2 The forest plots on the GrimAge components of note from meta-analyses for seven cohorts comparing patients with schizophrenia or first-episode psychosis, with controls, in the first regression model. A DNAmADM, **B** DNAmB2M, **C** DNAmCystatinC, and (**D**) DNAmPAI1. Figure creation and statistical calculations are performed using the R package metafor. Abbreviations: ADM adrenomedullin, B2M beta-2 microglobulin, DNAm DNA methylation, PAI1 plasminogen activation inhibitor-1.

cohorts (excluding first-episode psychosis) are listed in Supplementary Tables 14 and 15, respectively. In the meta-analyses of seven cohorts, AgeAccelHannum, AgeAccelGrim, AgeAccelGrim2, DNAmTLAdgAge, DunedinPACE, DNAmADM, DNAmCystatinC, DNAmPAI1, DNAmPACKYRS, and DNAmpai_1 showed significant differences between patients and controls (Supplementary Table 14). In the meta-analyses of five cohorts, AgeAccelGrim, AgeAccelGrim2, DNAmTLAdjAge, DunedinPACE, DNAmADM, DNAmCystatinC, DNAmPAI1, DNAmPACKYRS, DNAmadm, and DNAmpai_1 showed significant differences between patients and controls (Supplementary Table 15). We created forest plots the same way we did for the main analyses. For the meta-analyses integrating seven cohorts (including first-episode psychosis), forest plots of the epigenetic age acceleration are displayed in Supplementary Fig. 28 and GrimAge components in Supplementary Fig. 29. For the meta-analyses integrating five cohorts (excluding first-episode psychosis), forest plots of the epigenetic age acceleration are displayed in Supplementary Fig. 30 and GrimAge components in Supplementary Fig. 31.

The results of meta-analyses for only females integrating seven cohorts (including first-episode psychosis) or integrating five cohorts (excluding first-episode psychosis) are listed in Supplementary Tables 16 and 17, respectively. In the meta-analyses of seven cohorts, AgeAccelHannum, AgeAccelPheno, AgeAccelGrim, AgeAccelGrim2, DunedinPACE, DNAmADM, DNAmB2M, DNAmCystatinC, DNAmGDF15, DNAmPAI1, DNAmTIMP1, DNAmPACKYRS, DNAmadm, DNAmCystatin_C, DNAmGDF_15, and DNAmpai_1 showed significant differences between patients and controls (Supplementary Table 16). In the meta-analyses of five cohorts, AgeAccelHannum, AgeAccelPheno, AgeAccelGrim, AgeAccelGrim2, DunedinPACE, DNAmADM, DNAmB2M, DNAmCystatinC, DNAmGDF15, DNAmLeptin, DNAmPAI1, DNAmTIMP1, DNAmPACKYRS, DNAmadm, DNAmCystatin_C, DNAmGDF_15, DNAmleptin, and DNAmpai_1 showed significant differences between patients and controls (Supplementary Table 17). We created forest plots the same way we did for the main analyses. For the meta-analyses integrating seven cohorts (including first-episode psychosis), forest plots of the epigenetic age acceleration are displayed in Supplementary Fig. 32 and GrimAge components in Supplementary Fig. 33. For the meta-analyses

Table 2. Results of meta-analyses of five cohorts comparing patients with schizophrenia, excluding first-episode psychosis, and controls in the first regression model.

	Effect size (95% CI)	Standard error	*z*-value	*p*-value	I^2 (%)
Epigenetic age acceleration					
AgeAccelHorvath	−0.0137 (−0.1142–0.08681)	0.05128	−0.2671	0.7894	68.92855
AgeAccelHannum	0.0296 (−0.09748–0.15669)	0.06484	0.4565	0.6480	81.47102
AgeAccelSkinBlood	−0.03772 (−0.15239–0.07695)	0.05851	−0.6448	0.5191	76.06965
AgeAccelPheno	0.05406 (0.00594–0.10218)	0.02455	2.2018	***0.02768***	0.10564
AgeAccelGrim	0.07585 (0.05678–0.09491)	0.00973	7.7974	$\boldsymbol{6.320 \times 10^{-15}}$	0.33303
AgeAccelGrim2	0.08426 (0.05512–0.11341)	0.01487	5.6668	$\boldsymbol{1.455 \times 10^{-8}}$	30.99890
DNAmTLAdjAge	0.06776 (0.02121–0.11431)	0.02375	2.8531	$\boldsymbol{4.329 \times 10^{-3}}$	1.20983
DunedinPACE	0.14869 (0.07489–0.22249)	0.03765	3.9488	$\boldsymbol{7.853 \times 10^{-5}}$	69.37428
GrimAge component					
DNAmADM	0.06975 (0.04462–0.09489)	0.01283	5.4386	$\boldsymbol{5.370 \times 10^{-8}}$	0.00000
DNAmB2M	0.02386 (0.00508–0.04264)	0.00958	2.4906	***0.01275***	0.00000
DNAmCystatinC	0.05208 (0.03426–0.0699)	0.00909	5.7296	$\boldsymbol{1.007 \times 10^{-8}}$	0.00000
DNAmGDF15	0.02085 (−0.0038–0.04549)	0.01257	1.6580	0.09731	0.00000
DNAmLeptin	0.02325 (−0.00912–0.05562)	0.01652	1.4077	0.1592	0.00000
DNAmPAI1	0.11368 (0.06989–0.15747)	0.02234	5.0879	$\boldsymbol{3.621 \times 10^{-7}}$	0.00000
DNAmTIMP1	0.03287 (−0.00024–0.06599)	0.01689	1.9458	0.05168	83.59582
DNAmPACKYRS	0.44681 (0.38172–0.51191)	0.03321	13.453	$\boldsymbol{2.950 \times 10^{-41}}$	59.97047
GrimAge2 component					
DNAmadm	0.07382 (0.04654–0.1011)	0.01392	5.3036	$\boldsymbol{1.135 \times 10^{-7}}$	0.00000
DNAmCystatin_C	0.05785 (0.03579–0.07991)	0.01125	5.1407	$\boldsymbol{2.737 \times 10^{-7}}$	0.00000
DNAmGDF_15	0.02355 (−0.01009–0.05719)	0.01716	1.3723	0.1700	23.84953
DNAmleptin	0.02506 (−0.00732–0.05743)	0.01652	1.5169	0.1293	0.00000
DNAmpai_1	0.11353 (0.06974–0.15732)	0.02234	5.0810	$\boldsymbol{3.754 \times 10^{-7}}$	0.00000
DNAmTIMP_1	0.02251 (−0.03593–0.08095)	0.02982	0.7550	0.4502	89.55722

All values were calculated by meta-analyses using a random-effects model with standardized regression coefficients and standard errors for phenotypes in each cohort using the R package metafor. In these regression analyses, the first regression model was used.
The first regression model: Each item (Age acceleration, GrimAge component, or GrimAge2 component) ~ Phenotype (controls or patients) + Age + Sex + DNAmPACKYRS.
I^2 values were used to evaluate heterogeneity (0–40%, might not be important; 30–60%, may present moderate heterogeneity; 50–90%, may present substantial heterogeneity; 75–100%, considerable heterogeneity).
ADM adrenomedullin, *B2M* beta-2 microglbulin, *CI* confidence interval, *GDF15* growth differentiation factor-15, *PAI1* plasminogen activation inhibitor-1, *TIMP1* tissue inhibitor of metalloproteinases-1, *DNAm* DNA methylation, *DNAmPACKYRS* DNA methylation-based smoking pack-years, *DNAmTLadjAge* age-adjusted estimate of DNA methylation-based telomere length.
$p < 0.05$ are shown in bold and italic.

integrating five cohorts (excluding first-episode psychosis), forest plots of the epigenetic age acceleration are displayed in Supplementary Fig. 34 and GrimAge components in Supplementary Fig. 35.

The results of meta-analyses for participants under 40 years old integrating seven cohorts (including first-episode psychosis) or integrating five cohorts (excluding first-episode psychosis) are listed in Supplementary Tables 18 and 19, respectively. In the meta-analyses of seven cohorts, AgeAccelHannum, AgeAccelGrim, AgeAccelGrim2, DunedinPACE, DNAmADM, DNAmCystatinC, DNAmLeptin, DNAmPAI1, DNAmPACKYRS, DNAmadm, DNAmleptin, and DNAmpai_1 showed significant differences between patients and controls (Supplementary Table 18). In the meta-analyses of five cohorts, AgeAccelGrim, AgeAccelGrim2, DunedinPACE, DNAmADM, DNAmPAI1, DNAmPACKYRS, and DNAmpai_1 showed significant differences between patients and controls (Supplementary Table 19). We created forest plots the same way we did for the main analyses. For the meta-analyses integrating seven cohorts (including first-episode psychosis), forest plots of the epigenetic age acceleration are displayed in Supplementary Fig. 36 and GrimAge components in Supplementary Fig. 37. For the meta-analyses integrating five cohorts (excluding first-episode psychosis), forest plots of the epigenetic age acceleration are displayed in Supplementary Fig. 38 and GrimAge components in Supplementary Fig. 39.

DISCUSSION

To the best of our knowledge, this is the first study to integrate the epigenetic aging data, up to GrimAge and GrimAge2 components in patients with schizophrenia or first-episode psychosis in various cohorts. GrimAge and GrimAge2 outperform previous epigenetic clocks in their ability to predict mortality, coronary heart disease, and time to cancer[21,22]. We pay attention to the observed changes of acceleration in these epigenetic these clocks. The results corroborate findings that patients with schizophrenia have a higher prevalence of diseases, such as cardiovascular disease and diabetes, and a shorter life expectancy than the general population[43,44].

ADM is widely expressed in the brain and highly associated with the central nervous system (CNS) function. In mice, an ADM deficiency in the CNS results in hyperactivity, increased anxiety, and increased susceptibility to the neurotoxic effects of hypoxia[45]. ADM is also associated with bipolar disorder and major depressive

disorder[33,34]. Cystatin C is a well-known biomarker of renal dysfunction[43,46]. Cystatin C levels are reported to be associated with depression and suicidal ideation[35,44]. Although few studies have examined the association between cystatin C levels and schizophrenia or related diseases, the fact that patients with schizophrenia exhibit a lack of motivation[47], depression[48], and cognitive deficits, such as social cognition[36], makes the involvement of cystatin C levels noteworthy. PAI1 is a major physiological inhibitor of tissue plasminogen activator in the plasma and is increased in several clinical situations related to ischemic cardiovascular events and aging[49,50]. Elevated PAI1 levels have adverse effects on brain neurons[51–53]. We have previously shown that the predictive value of PAI1 by DNAm was significantly higher in patients with autism spectrum disorders than in healthy controls[54]. Schizophrenia or related diseases have similar parts to autism spectrum disorders in terms of both symptoms and genetics[55].

In the second regression model that included white blood cell compositions as confounding factors, the effect sizes of the disease on epigenetic age acceleration, GrimAge components, and GrimAge2 components were generally lower than those in the first regression model. However, among the explanatory variables in the second regression model, the many white blood cell compositions showed multicollinearity. Further, the white blood cell compositions themselves change with age[56]. These possibly have led to underestimation of the effect sizes. In the subgroup analysis, the effect sizes of the disease on the epigenetic age acceleration, GrimAge components, and GrimAge2 components were generally stronger in females than in males. A systematic review reported that females are more likely to experience side effects from antipsychotic drugs[57], and other reports suggest females with schizophrenia have a higher incidence of cardiovascular disease and diabetes[58–60]. In addition, a study reported that among patients with schizophrenia, females were more likely than males to have impaired working memory and problem-solving skills[61].

This study found differences between patients with schizophrenia and first-episode psychosis when compared to controls. The effect sizes were generally higher and I^2 values lower when excluding first-episode psychosis. Higher I^2 values indicated higher heterogeneity among the studies, leading to less consistent results. First-episode psychosis is likely associated with a shorter disease duration. Several studies have suggested that a longer duration of schizophrenia increases the risk of physical diseases, such as diabetes[62,63]. Although antipsychotic medications increase the risk of physical diseases, such as diabetes and cardiovascular diseases[64], at least for the Japan cohort in this study, most patients with schizophrenia had no history of antipsychotic use. Rather than antipsychotic drugs, patients with schizophrenia have multiple risk factors for physical disorders, such as low socioeconomic status, cognitive dysfunction, poor diet, and genetic homology with diseases, such as diabetes[65,66]. However, patients with first psychotic episodes have various outcomes[67]. Appropriate early interventions often improve cognitive function[68]. It is possible that the differences between the results of this study in patients with schizophrenia and those with first-episode psychosis reflect differences in the prognosis and pathology of the diseases themselves.

Ori et al. has reported that AgeAccelPheno were associated with high polygenic risk scores for schizophrenia, which is calculated using genome-wide SNP data[69,70]. Although we were unable to obtain the genome-wide SNP data of the participants in this study, we considered the research stratified by polygenic risk score is also very meaningful. By combining comprehensive genomic and epigenomic data, we may obtain results with more details.

It is well known that the neighborhood environment has various effects on human health. Epigenetic Age is an effective predictor of age-related health conditions, and is also related to the neighborhood environment[71]. In addition, neighborhood environments having social division are linked to a higher risk of developing psychiatry diseases, including schizophrenia[72]. Epigenetic age acceleration and risk of schizophrenia have this common environment factor, thus it is not difficult to imagine that epigenetic age tends to accelerate in schizophrenia patients.

Our study has some limitations. First, patients who are hospitalized for long periods of time or repeatedly, often eat a hospital-balanced diet, may have a deceleration of their biological age compared with other patients. Further, we could not obtain information such as alcohol consumption and body mass index, which affects DNAm. These factors may also have impacts on the heterogeneity between cohorts. Second, the components of GrimAge and GrimAge2 were predicted based on DNAm profiles. The proteins selected for the GrimAge components have relatively higher correlation between measured and predicted values, but even these correlation coefficients are not very high, ranging from 0.35 to 0.53[21]. Therefore, it is important to confirm the actual values to validate our results. In addition, we were unable to obtain predictive values for HbA1c and CRP, which are among GrimAge2 components. Furthermore, since no information on actual smoking history was available, DNAmPACKYRS was used as a confounding factor in the multiple regression analyses as an indicator of smoking history. There were significant differences in DNAmPACKYRS between patients and controls, but this would not be a disease-specific finding, considering the high rate of smoking in patients with schizophrenia[8]. Third, there were no cohorts including both of patients with schizophrenia and first-episode psychosis, with the information of age and sex; therefore, we could not compare them directly. Fourth, in this study, we used multiple regression analyses in order to consider multiple confounding factors, but we could not prove the normality or homogeneity of variance of the data. Further, the effect sizes themselves were quite modest even in items showing significance.

Despite these limitations, this study provides biological support for aging and increased mortality in patients with schizophrenia or related diseases, captures some of the factors responsible for aging, and may lead to the development of further studies and therapeutic targets in the future. Furthermore, we believe that this study can be combined with examinations based on the fields such as genomics and environmental studies to develop into future studies with more detail.

METHODS

Japanese participants (Japan cohorts)

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committees of Kobe University Graduate School of Medicine and University of Tokushima Graduate School. Written informed consent was obtained from all the participants after they received a complete description of the study.

The Japan cohort consisted of 24 patients with schizophrenia and 23 healthy controls recruited from Tokushima University. Among these patients, 16 had no history of taking antipsychotics; among the remaining patients, seven had not taken any antipsychotics for at least 2 months. The patients' demographic and clinical characteristics are shown in Supplementary Table 1.

Psychiatric assessments were performed as previously described[73]. A diagnosis of schizophrenia was established by at least two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) criteria for schizophrenia based on unstructured interviews and reviews of their medical records. Control participants were healthy volunteers screened by a psychiatrist for psychiatric disorders. None of the participants had a present, past, or family (first-degree relatives)

history of psychiatric disorders or substance abuse, excluding nicotine dependence. In both cohorts, all participants were of Japanese descent.

Publicly available DNAm datasets (GSE41169, GSE80417, GSE84727, GSE147221, GSE152026, and GSE152027 cohorts)

Replication analyses were performed using six independent DNAm datasets (GSE41169, GSE80417, GSE84727, GSE147221, GSE152026, and GSE152027) downloaded from the Gene Expression Omnibus database. We used the data of participants that included information of age and sex, within the datasets. The GSE41169, GSE80417, GSE84727, GSE147221, and GSE152027 datasets contained blood DNAm data obtained using Illumina Infinium HumanMethylation450 BeadChip array. GSE152026 blood DNAm data were obtained using methylation EPIC array. The GSE41169 cohort was generated using the GSE41169 dataset of ref. [74], consisting of 62 patients with schizophrenia and 33 controls from the University Medical Center Utrecht in the Netherlands. The GSE80417 dataset was generated by Hannon et al.[75,76] and consisted of participants from the University College London in England. After excluding participants with missing or erroneous chronological age information, as described by McKinney et al.[77], analyses were performed on 332 patients with schizophrenia and 304 controls in the GSE80417 cohort. Schizophrenia was diagnosed according to the International Statistical Classification of Diseases and Related Health Problems 10th edition (ICD-10). The GSE84727 dataset was generated by Hannon et al.[75], consisting of samples from the University of Aberdeen in Scotland[78]. Diagnoses of schizophrenia were established according to the DSM-IV and ICD-10. After excluding participants with missing chronological age information, analysis was performed on 260 patients with schizophrenia and 405 controls as the GSE84727 cohort. The GSE147221 dataset was generated by Hannon et al.[79,80] and consisted of participants from the University of Dublin, Ireland. Diagnoses of schizophrenia were established according to the DSM-IV. After excluding participants with missing chronological age information, analysis was performed on 348 patients with schizophrenia and 331 controls as the GSE147221 cohort. The GSE157026 dataset was generated by Hannon et al.[79,80], consisting of samples from the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions cohort. Patients with first-episode psychosis were diagnosed using the ICD-10. After excluding participants with missing chronological age information, analysis was performed on 519 patients with first-episode psychosis and 409 controls as the GSE157026 cohort. The GSE157027 dataset was generated by Hannon et al.[79,80] and consisted of participants from the Institute of Psychiatry, Psychology, and Neuroscience. Patients with first-episode psychosis were diagnosed using the ICD-10. After excluding participants with missing chronological age information, analysis was performed on 277 patients with first-episode psychosis and 194 controls as the GSE157027 cohort. The demographic and clinical characteristics are shown in Supplementary Table 1.

Evaluation of epigenetic clocks, DNAm-based telomere length, epigenetic age acceleration, and DNAm-based aging-related factors

Blood samples were subjected to DNA extraction, and DNAm percentages calculated via bisulfite transformation. We calculated epigenetic age with six epigenetic clocks (HorvathAge, HannumAge, SkinBloodAge, PhenoAge, GrimAge, and GrimAge2), DNAmTL, GrimAge components (ADM, B2M, cystatin C, GDF15, leptin, PAI1, TIMP1, and DNAmPACKYRS), and GrimAge2 components (ADM, cystatin C, GDF15, leptin, PAI1, and TIMP1) using online DNAm age calculator (https://horvath.genetics.ucla.edu/html/dnamage/ last accessed August 20, 2023) with DNAm statuses[17]. We evaluated epigenetic age acceleration: AgeAccelHorvath, AgeAccelHannum, AgeAccelSkinBlood, AgeAccelPheno, AgeAccelGrim, and AgeAccelGrim2 were defined as the residual from regressing each DNAm age on the chronological age. Positive and negative values indicated whether the epigenetic age was higher or lower than the expected age (based on chronological age), respectively. The DNAmTLadjAge was defined as the residual calculated by regressing DNAmTL on the chronological age. Positive and negative values indicated whether DNAmTLadjAge was longer or shorter than the expected DNAmTL, respectively. We calculated DunedinPACE using the R package DunedinPACE. Regarding GrimAge and GrimAge2 components, to be consistent with the notation in the online calculator, the GrimAge components were denoted as DNAmADM, DNAmB2M, DNAmCystatinC, DNAmGDF15, DNAmLeptin, DNAmPAI1, DNAmTIMP1, and DNAmPACKYRS, while the GrimAge2 components were denoted as DNAmadm, DNAmCystatin_C, DNAmGDF_15, DNAmleptin, DNAmpai_1, and DNAmTIMP_1. Furthermore, in this calculator, multiple white blood cell compositions (CD8+ T cell, CD4+ T cell, Natural killer cell, B cell, Monocyte, Granulocyte, and PlasmaBlast) were also predicted based on comprehensive DNAm status[81].

Statistical analyses

Statistical analyses were performed using R version 4.2.1 (R Development Core Team, Vienna, Austria). For demographic data, categorical variables were analyzed using Fisher's exact test, and between-group differences in continuous variables were analyzed using the Mann–Whitney *U* test. We conducted standardized regression analysis using two regression models. All variables were standardized when conducting the regression analyses. We checked the normality of the distribution with the Kolmogorov-Smirnov test and the equality of variances with the F test. In the first regression model, we used epigenetic age accelerations and GrimAge and GrimAge2 components of each cohort as objective variables; phenotype (patients or controls) as explanatory variables; and age, sex, and smoking history as confounding factors. In the second regression model, we added predictive values of white blood cell compositions (CD8+ T cell, CD4+ T cell, Natural killer cell, B cell, Monocyte, Granulocyte, and PlasmaBlast) based on DNAm status as additional confounding factors. As information on actual smoking history could not be obtained, DNAmPACKYRS values, which are predictive of cumulative smoking status based on DNAm, were used instead of smoking history. However, in the multiple regression analysis with DNAmPACKYRS as the objective variable, we have not used DNAmPACKYRS as confounding factor. The results of each cohort were combined in the meta-analyses using the R package metafor. In addition to the meta-analyses of seven cohorts comparing patients with schizophrenia or first-episode psychosis to controls, we performed meta-analyses of five cohorts comparing only patients with schizophrenia, excluding first-episode psychosis, to controls as well as meta-analyses of two cohorts comparing only patients with first-episode psychosis to controls using a mixed-effects model. Additionally, we conducted subgroup analyses, against only males, only females, and participants under 40 years old, using the first regression model and conducted meta-analyses integrating seven cohorts (including first-episode psychosis) and five cohorts (excluding first-episode psychosis). I^2 values were used to evaluate heterogeneity (0–40%, might not be important; 30–60%, may present moderate heterogeneity; 50–90%, may present substantial heterogeneity; 75–100%, considerable heterogeneity). Statistical significance was defined as a two-tailed $p < 0.05$.

Dummy variables were used where needed: for sex, male = 1 and female = 2; for phenotype, controls = 1 and patients = 2. We created the forest plot showing the results of the meta-analyses with the R package metafor.

DATA AVAILABILITY

Data for the Japan cohort are available upon request. The GSE41169, GSE80417, GSE84727, GSE147221, GSE152026, and GSE152027 cohorts are publicly available from the Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE41169, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE80417, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE84727, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE147221, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE152026, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE152027).

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T.S.: Data curation, Formal analysis, Investigation, Visualization, and Writing—original draft. S.O.: Conceptualization, Methodology, Data curation, Formal analysis, and Writing—review & editing. T.T.: Data curation and Formal analysis. S.N.: Investigation and Resources. T.N.: Investigation and Resources. T.Y.: Investigation and Resources. K.M.: Data curation and Formal analysis. I.O.: Data curation and Formal analysis. N.H.: Supervision and Writing—review & editing. A.H.: Conceptualization, Supervision, and Writing—review & editing.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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