Biological Psychiatry

Archival Report

Accelerated Pace of Aging in Schizophrenia: Five Case-Control Studies

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ABSTRACT

BACKGROUND: Schizophrenia is associated with increased risk of developing multiple aging-related diseases, including metabolic, respiratory, and cardiovascular diseases, and Alzheimer s and related dementias, leading to the hypothesis that schizophrenia is accompanied by accelerated biological aging. This has been dif cult to test because there is no widely accepted measure of biological aging. Epigenetic clocks are promising algorithms that are used to calculate biological age on the basis of information from combined cytosine-phosphate-guanine sites (CpGs) across the genome, but they have yielded inconsistent and often negative results about the association between schizophrenia and accelerated aging. Here, we tested the schizophrenia-aging hypothesis using a DNA methylation measure that is uniquely designed to predict an individual s rate of aging.

METHODS: We brought together 5 case-control datasets to calculate DunedinPACE (Pace of Aging Calculated from the Epigenome), a new measure trained on longitudinal data to detect differences between people in their pace of aging over time. Data were available from 1812 psychosis cases (schizophrenia or rst-episode psychosis) and 1753 controls. Mean chronological age was 38.9 (SD = 13.6) years.

RESULTS: We observed consistent associations across datasets between schizophrenia and accelerated aging as measured by DunedinPACE. These associations were not attributable to tobacco smoking or clozapine medication.

CONCLUSIONS: Schizophrenia is accompanied by accelerated biological aging by midlife. This may explain the wide-ranging risk among people with schizophrenia for developing multiple different age-related physical diseases, including metabolic, respiratory, and cardiovascular diseases, and dementia. Measures of biological aging could prove valuable for assessing patients risk for physical and cognitive decline and for evaluating intervention effectiveness.

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Individuals who develop schizophrenia are at risk of developing multiple diseases, including type 2 diabetes (1), respiratory disease (2), cardiovascular disease (3,4), and Alzheimer s disease and related dementias (5–7). The medical conditions that postdate schizophrenia are all known to markedly increase in incidence with advancing age. Not only do older adults with schizophrenia show increased risk for these medical conditions, but the medical conditions also show precocious onset among younger adults with schizophrenia. This observation has led to the hypothesis that schizophrenia is accompanied by accelerated biological aging (8,9), or even more radically, that schizophrenia is itself a syndrome of accelerated aging (10).

It is dif cult to test the hypothesis that schizophrenia is associated with accelerated aging because there is no widely accepted outcome measure of biological aging (11,12). However, progress on this front has been rapid, most notably including efforts to measure individual differences in the pace of aging using omics data, especially genome-wide DNA methylation data (13). DNA methylation is an epigenetic mechanism involving the chemical modi cation of cytosine that influences the regulation of gene expression. Many efforts to develop measures of aging have focused on blood DNA methylation because blood is the most widely pro led source of DNA, and blood DNA methylation is a biological substrate that is sensitive to age-related changes at the level of the whole body (14,15). Using machine learning, these measurement efforts develop algorithms to capture information about aging by combining DNA methylation levels from many different sites across the genome. First-generation DNA methylation algorithms were trained on birth year in samples comprising people ranging from children to older adults. These clocks identi ed methylation patterns that vary by chronological age, i.e., time elapsed since birth. If such clocks estimate a person s age as older than his/her actual chronological age, it is inferred that he or she is biologically older. First-generation algorithms include the Horvath clock (16) and the Hannum clock (17). Second-generation DNA methylation algorithms added measures of people s current physiological status to identify methylation patterns that account for differences in current health and that predict mortality. Second-generation algorithms include PhenoAge (18) and GrimAge (19). Tests of the association between schizophrenia and accelerated aging using these clocks have yielded inconsistent and mostly negative results (20–26).

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In contrast to earlier algorithms that relied on cross-sectional point-in-time measures of current health to estimate biological age (18,19), we recently developed a DNA methylation measure that is unique in estimating an individual s rate of aging. The DunedinPACE (Pace of Aging Calculated from the Epigenome) algorithm was developed by rst measuring people s rates of physiological decline in the functions of multiple organ systems over years of time with repeated longitudinal assessments and then identifying the methylation patterns that captured differences between individuals in the steepness of their slopes of age-related whole-body decline. Speci cally, we measured age-related change in 19 cardiovascular, metabolic, renal, immune, dental, and pulmonary biomarkers over a 20-year observation period in a birth cohort of individuals who were all the same chronological age in the Dunedin Longitudinal Study (27). Then, we identi ed a methylation pattern at the end of the observation period that estimates how fast aging has occurred during the years leading up to the point of measurement (28). Thus, DunedinPACE was designed to capture methylation patterns that reflect individual differences in age-related whole-body decline. An attractive feature of DunedinPACE is that it now makes it possible to measure the pace of aging in individuals who lack data to implement longitudinal physiological pro ling. This new measurement tool has been shown to predict age-related disability, morbidity, cognitive decline, dementia, and mortality by our team (28,29) and others (30–34). DunedinPACE is useful as a measure of biological aging across much of the life span, has been exported to scores of cohorts, and has been used with diverse ethnic groups (35,36). It can now be exported to diverse case-control studies of schizophrenia that have DNA methylation data to test the hypothesis that schizophrenia is associated with accelerated aging, this time using this newer measure that may yield more consistent results than rst- and second-generation clocks.

Here, we leveraged data from 5 case-control datasets (3500 individuals) to examine whether individuals diagnosed with psychosis (rst-episode psychosis or con rmed schizophrenia) were aging at a faster rate than controls. In each study, we evaluated each individual s pace of aging by applying the DunedinPACE algorithm to their genome-wide DNA methylation data. We studied young and middle-aged adults (average chronological age = 38.9 years, SD = 13.6) rather than older adults for two reasons. First, studying young and middle-aged adults allowed us to avoid bias from selective death because individuals with schizophrenia die 10 years younger on average than people in the general population (37–39). Second, studying young and middle-aged adults generates ndings that can inform midlife interventions to prevent diseases before they onset in later life (40).

To clarify ndings, we evaluated whether psychosis is associated with accelerated aging merely because both are associated with tobacco smoking. Individuals with schizophrenia are known to consume tobacco products at a high rate (41), and exposure to tobacco smoking is known to be associated with accelerated aging (42). Second, we tested whether accelerated aging is already apparent among individuals experiencing rst-episode psychosis or more apparent among individuals who have a con rmed diagnosis of schizophrenia. After the rst episode, people with schizophrenia experience degeneration in neurological and physical function. Thus, accelerated aging may be apparent in con rmed schizophrenia but not yet at rst episode. Third, we evaluated the possibility that the association between schizophrenia and accelerated aging is due to medication side effects. Although antipsychotic medications are effective in preventing relapse in schizophrenia, it is thought that their long-term use may harm patients physical health (43,44). Here, we tested whether patients who were prescribed clozapine were aging at a faster rate than patients who were not taking clozapine. Clozapine is typically prescribed after other antipsychotics have failed; thus, it tends to indicate a longer-term medication experience.

METHODS AND MATERIALS

Dataset Descriptions

The 5 datasets used in this study, which included those from University College London (UCL), Aberdeen, Dublin, Institute of Psychiatry, Psychology, and Neuroscience (IoPPN), and the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI), are from publicly available studies gathered for a recent epigenome-wide association study of psychosis (45). Dataset details are also provided in the Supplement. To be included in this study, a dataset was required to have information about participants case-control status, sex, and age, as well as high-quality DNA methylation data. For this reason, in some datasets, sample sizes and descriptive statistics differ from those reported in Hannon *et al* (45).

UCL Dataset. Schizophrenia cases and controls were participants from the UCL schizophrenia dataset. Data were available for 304 schizophrenia cases and 332 controls. Raw and processed data are available through Gene Expression Omnibus (GEO) accession number GSE84727.

Aberdeen Dataset. Schizophrenia cases and controls were participants from the Aberdeen schizophrenia dataset. Data were available for 260 schizophrenia cases and 405 controls. Raw and processed data are available through GEO accession number GSE80417.

Dublin Dataset. Schizophrenia cases and controls were participants from the Irish Schizophrenia Genomics Consortium. Data were available for 331 schizophrenia cases and 348 controls. Raw and processed data are available through GEO accession number GSE147221.

IoPPN Dataset. The IoPPN dataset comprises schizophrenia cases, rst-episode psychosis cases, and nonpsychiatric controls recruited from the same geographical area into 3 studies via the South London & Maudsley Mental Health NHS Foundation Trust. Data were available for 206 schizophrenia cases, 278 rst-episode psychosis cases, and 194 controls. Raw and processed data are available through GEO accession number GSE152027.

EU GEI Dataset. First-episode psychosis cases and controls were participants from the incidence and case-control

work package of the EU-GEI. Data were available for 388 first-episode cases and 519 controls. Raw and processed data are available through GEO accession number GSE152026.

DNA Methylation Data

Genome wide Quantification of DNA Methylation. DNA methylation data were generated and processed at the University of Exeter, as described previously (45). Briefly, 500 ng of blood-derived DNA from each sample was treated with sodium bisulfite using the EZ-96 DNA methylation kit (Zymo Research). DNA methylation was quantified using either the Illumina Infinium HumanMethylation450 BeadChip (Illumina Inc.) or Illumina Infinium HumanMethylationEPIC BeadChip (Illumina Inc.) run on an Illumina iScan System (Illumina Inc.) using the manufacturer's standard protocol. Samples were batched by dataset and randomly assigned to ensure equal distribution of cases and controls across each array. Raw data were processed with the R programming environment using the *methylumi* (46), *minfi* (47), and *wateRmelon* (48) packages following our standardized pipeline. Normalization of the DNA methylation data was performed used the *dasen* function in the *wateRmelon* package (48).

Derivation of DunedinPACE and Epigenetic Clock Estimates. The primary outcome variable was accelerated pace of aging as measured by DunedinPACE, calculated using publicly available code (https://github.com/danbelsky/DunedinPACE) (28). It was then standardized to have a mean of 0 and an SD of 1 within each dataset. We also report secondary analyses of 4 other frequently reported measures of epigenetic age: Horvath and Hannum DNA methylation age clocks, PhenoAge, and GrimAge. The Horvath and Hannum clocks and PhenoAge were calculated using the *agep*() function in the *wateRmelon* package (48). The coefficients for Horvath and Hannum are available through the *wateRmelon* package, whereas for PhenoAge they were extracted from Supplement 2 of Levine *et al* (18) and provided to the function. GrimAge was calculated using the code in https://github.com/MorganLevineLab/PC-Clocks using the associated reference data; this is the publicly available version of GrimAge as described in Higgins-Chen *et al* (49). DunedinPACE yields an estimate in years of physiological age acceleration per 1 chronological year. In contrast, the 4 clock algorithms yield an estimate of chronological age, and therefore they must be transformed to yield an estimate of age acceleration. We transformed all DNA methylation measures into measures of accelerated aging by taking the residuals from a linear model in which each of the DNA methylation measures was regressed on chronological age. The resulting age-acceleration measurements were then standardized to have a mean of 0 and an SD of 1 to ensure comparability across clock predictions. This was performed separately for each clock and each dataset.

Estimating Cell Count Information and Tobacco Smoking History Using DNA Methylation Data. Because cell count data were not available for all datasets, we estimated cell proportions (monocytes, CD8 T cells, CD4 T cells, B cells, and granulocytes) from the DNA methylation data using the Houseman reference-based algorithm (50,51). Similarly, because self-reported tobacco smoking and body mass index (BMI) were incomplete across datasets, we calculated proxies from the DNA methylation data: A tobacco exposure score was calculated using the method described by Elliott *et al* (52) and used in our previous analyses (53) and a BMI score using the method described by Hamilton *et al* (54).

Statistical Analysis

The primary outcome variable was individuals' pace of aging as measured by DunedinPACE. Linear regression models were used to test the association between psychosis status and accelerated pace of aging using the *lm* function in R. Four different analytical models were fitted in which standardized DunedinPACE was regressed against a binary psychosis status variable, with the incremental inclusion of additional covariates, as follows:

1. DunedinPACE ~ psychosis
2. DunedinPACE ~ psychosis + sex + age
3. DunedinPACE ~ psychosis + sex + age + cell proportions
4. DunedinPACE ~ psychosis + sex + age + cell proportions + smoking score

We included cell counts because it is expected that variation in white blood cell type abundance will be controlled for in epigenetic research due to the potential for confounding. We included tobacco smoking because individuals with schizophrenia consume tobacco products at a high rate compared with controls, and tobacco exposure is known to be associated with accelerated aging. For each model, results across the 5 datasets were combined using a fixed-effects meta-analysis implemented with the *metagen* function from the R package *meta* (55). The input from each dataset was the estimated effect size (i.e., difference in the pace of aging between patients with psychosis and controls) and its associated standard error. These effect sizes were combined into a weighted pooled estimate and standard error from which a *p* value was calculated. All reported *p* values are from 2-tailed tests. The results from random-effects models are also presented as a robustness check. In addition, we conducted 3 sensitivity analyses in which we added the following covariates to regression models in each dataset: batch covariates (i.e., DNA methylation chip), covariates for the first 2 genetic principal components (Figure S1), and a BMI epigenetic proxy. Parallel to the meta-analysis that synthesized the results of analyses from the 5 datasets, we also conducted a mega-analysis in which we pooled the individual-level data from all 5 datasets into a single mixed-effects regression model with dataset included as a random effect.

We used the 5 datasets to further test differences in the pace of aging between 1) first-episode psychosis patients and controls, 2) confirmed schizophrenia cases and controls, and 3) drug-treated patients with schizophrenia (defined by the prescription of clozapine) and patients with schizophrenia who were not taking clozapine (most of whom were taking other medications). The groups used in these comparisons have been described previously (45). For each of these 3 follow-up analyses, we estimated regression model 4 as outlined

above and then meta-analyzed the resulting effect sizes as described above.

In secondary analyses, we repeated the primary analysis strategy using the age-acceleration residuals from the 4 epigenetic age clock algorithms (Horvath, Hannum, PhenoAge, GrimAge) as the outcome measures.

RESULTS

Data were available for 3565 (63 male) individuals, comprising 1812 psychosis cases (schizophrenia or rst-episode psychosis) and 1753 controls. Table 1 shows that 68 (1229) of the psychosis cases were male, compared with 59 (1028) of the controls. On average, cases were slightly younger than controls (mean = 38.3 years, SD = 13.7 vs. mean = 39.5 years, SD = 13.5). As expected, psychosis cases were characterized by a more pronounced DNA methylation signature of tobacco smoking than controls (mean = 6.31, SD = 6.36 vs. mean = 2.43, SD = 5.26).

DunedinPACE is measured in years of physiological decline per 1 chronological year. Table 2 shows that psychosis cases were characterized by a signi cantly faster pace of aging than controls in 4 of the 5 datasets. EU-GEI, comprising only rst-episode cases, was the sole dataset that did not show a faster pace of aging among cases versus controls. Across the 5 datasets, cases with psychosis aged, on average, 1.01 months/year faster than controls. This represents a moderate-to-large meta-analysis effect size (0.65, 95 CI, 0.59 to 0.71 SD units) (Table S1). Figure 1 presents the forest plot of associations between psychosis and DunedinPACE. In this analysis, the estimated effects represent the mean difference between psychosis cases and healthy controls, in units of SD, after controlling for sex, age, cellular compositions (proportion of monocytes, CD8 T cells, CD4 T cells, B cells, and granulocytes), and tobacco smoke exposure. Across the 5 datasets, psychosis remained signi cantly associated with a faster pace of aging (meta-analysis effect size = 0.22, 95 CI, 0.16 to 0.27). The association remained after introducing additional covariates indexing batch, genetic principal components, and BMI (Table S2). A mega-analysis in which we pooled the individual-level data from all 5 datasets into 1 analysis yielded a similar effect size, 0.21, 95 CI, 0.15 to 0.26 (Table S3).

We conducted 3 follow-up analyses and included the same 4 covariates. First, we compared rst-episode psychosis patients with controls, excluding cases of schizophrenia from the analysis. Results were mixed. First-episode psychosis patients in the IoPPN dataset exhibited a signi cantly accelerated pace of aging, but rst-episode psychosis patients in the EU-GEI dataset did not, yielding a nonsigni cant association overall (meta-analysis effect size = 0.08, 95 CI, −0.01 to 0.16) (Figure 2A). Second, we compared con rmed schizophrenia cases with controls, excluding cases of rst-episode psychosis from the analysis. Schizophrenia was robustly associated with a faster pace of aging (meta-analysis effect size = 0.31, 95 CI, 0.24 to 0.38) (Figure 2B). Third, we compared patients with schizophrenia who were prescribed clozapine with patients who were not taking clozapine in the 3 datasets where this information was available. The two groups did not differ in their pace of aging, suggesting that among patients diagnosed with schizophrenia in these datasets, clozapine was not associated with accelerated aging (meta-analysis effect size = 0.03, 95 CI, −0.09 to 0.16) (Figure 2C).

Table 1. Summary of Demographics by Dataset

	Datasets					
Characteristics	UCL	Aberdeen	Dublin	IoPPN	EU-GEI	Total
No. of Subjects						
Total, *N*	636	665	679	678	907	3565
Controls, *n*	304	405	331	194	519	1753
Psychosis cases, *n*	332	260	348	484	388	1812
Schizophrenia cases, *n*	332	260	348	206	NA	1146
First-episode cases, *n*	NA	NA	NA	278	388	666
Sex, Male						
Controls, *n*	135	303	233	113	244	1028
Psychosis cases, *n*	242	178	249	310	250	1229
^{2} test *p* value	5.11×10^{-13}	.09	.80	.19	2.68×10^{-7}	1.58×10^{-8}
Age, Years, Mean (SD)						
Controls	36.8 (14.7)	44.9 (12.2)	42.0 (12.1)	30.3 (9.95)	38.7 (13.4)	39.5 (13.5)
Psychosis cases	43.7 (14.6)	44.2 (14.1)	41.4 (11.9)	35.2 (12.6)	30.7 (10.4)	38.3 (13.7)
t test *p* value	6.55×10^{-9}	.53	.51	1.39×10^{-7}	1.24×10^{-22}	7.49×10^{-3}
DNA Methylation Smoking Score, Mean (SD)						
Controls	0.31 (4.62)	7.65 (4.53)	2.11 (3.83)	2.53 (4.2)	−0.25 (4.23)	2.43 (5.26)
Psychosis cases	6.68 (5.98)	11.1 (5.37)	6.82 (6.25)	6.51 (6.09)	2.06 (4.88)	6.31 (6.36)
t test *p* value	4.13×10^{-44}	4.98×10^{-17}	1.92×10^{-29}	1.21×10^{-20}	2.48×10^{-13}	1.06×10^{-83}

EU-GEI, European Network of National Schizophrenia Networks Studying Gene-Environment Interactions; IoPPN, Institute of Psychiatry, Psychology, and Neuroscience; NA, not applicable; UCL, University College London.

Table 2. Association Between Psychosis and Accelerated Pace of Aging in Five Datasets

	Controls		Psychosis Cases		Schizophrenia Cases		First-Episode Psychosis Cases	
Datasets	Mean (SD)	95 CI	Mean (SD)	95 CI	Mean (SD)	95 CI	Mean (SD)	95 CI
DunedinPACE Raw Scores								
UCL	0.99 (0.12)	0.98 to 1.00	1.13 (0.14)	1.11 to 1.15	1.13 (0.14)	1.11 to 1.15	NA	NA
Aberdeen	1.05 (0.11)	1.04 to 1.06	1.15 (0.13)	1.13 to 1.17	1.15 (0.13)	1.13 to 1.17	NA	NA
IoPPN	0.97 (0.12)	0.95 to 0.99	1.07 (0.15)	1.06 to 1.08	1.13 (0.15)	1.11 to 1.15	1.02 (0.13)	1.00 to 1.04
Dublin	0.97 (0.12)	0.96 to 0.98	1.10 (0.13)	1.09 to 1.11	1.10 (0.13)	1.09 to 1.11	NA	NA
EU-GEI	0.98 (0.13)	0.97 to 0.99	0.98 (0.13)	0.97 to 0.99	NA	NA	0.98 (0.13)	0.97 to 0.99
DunedinPACE Standardized Scores								
UCL	−0.51 (0.78)	−0.60 to 0.42	0.47 (0.94)	0.37 to 0.57	0.47 (0.94)	0.37 to 0.57	NA	NA
Aberdeen	−0.31 (0.87)	−0.39 to 0.23	0.48 (1.01)	0.36 to 0.60	0.48 (1.01)	0.36 to 0.6	NA	NA
IoPPN	−0.47 (0.80)	−0.58 to 0.36	0.19 (1.01)	0.10 to 0.28	0.64 (0.99)	0.50 to 0.78	−0.15 (0.89)	−0.26 to −0.04
Dublin	−0.47 (0.84)	−0.56 to 0.38	0.44 (0.93)	0.34 to 0.54	0.44 (0.93)	0.34 to 0.54	NA	NA
EU-GEI	−0.01 (0.99)	−0.10 to 0.08	0.01 (1.01)	−0.09 to 0.11	NA	NA	0.01 (1.01)	−0.09 to 0.11

Pace of aging was measured using the DNA methylation–derived estimate, DunedinPACE, with higher scores indicating faster aging. DunedinPACE is measured in years of physiological decline per 1 chronological year. Scores were standardized to have a mean of 0 and an SD of 1 within each dataset.

DunedinPACE, Pace of Aging Calculated from the Epigenome; EU-GEI, European Network of National Schizophrenia Networks Studying Gene-Environment Interactions; IoPPN, Institute of Psychiatry, Psychology, and Neuroscience; NA, not applicable; UCL, University College London.

Secondary Analyses

In secondary analyses, we compared psychosis cases and controls on measures of age acceleration derived from 4 epigenetic clock algorithms (Table S2). Figure 3 shows the estimated effects, which represent the mean difference between psychosis cases and healthy controls, in units of SD, after controlling for sex, age, cellular composition (proportion of monocytes, CD8 T cells, CD4 T cells, B cells, and granulocytes), and tobacco exposure (see also Table S2). Psychosis was not robustly associated with the first-generation Horvath (meta-analysis effect size = 0.08, 95 CI, 0.00 to 0.15) and Hannum (meta-analysis effect size = 0.07, 95 CI, 0.01 to 0.14) epigenetic clocks or with the second-generation PhenoAge (meta-analysis effect size = 0.04, 95 CI, −0.03 to 0.11) and GrimAge (meta-analysis effect size = 0.02, 95 CI, −0.01 to 0.05) clocks (Figure 3B–E). In the latter case especially, initially apparent differences between psychosis cases and healthy controls were greatly diminished and not statistically significant after adjusting for tobacco smoking (Table S1). DunedinPACE stood out for its robust association with psychosis (Figure 3A); that is, the association effect size with DunedinPACE was approximately 3 times the size of the associations with other epigenetic clocks, and it yielded consistent and statistically significant estimates across multiple, independent datasets in both fixed- and random-effects meta-analysis models and in a mega-analysis.

DISCUSSION

Biological aging is conceptualized as the gradual and progressive deterioration of the whole body's biological system integrity across years of time, which increases vulnerability to multiple different age-related diseases later in life (56–58). Previous studies that have tested the association between schizophrenia and accelerated biological aging, as measured by the Horvath, Hannum, PhenoAge, and GrimAge epigenetic aging clocks, have yielded negative or inconsistent results (20–26). Some of these previous reports have used some data that overlap with the current report (20,22,23). In contrast, we report associations that are consistent across datasets between psychosis/schizophrenia and accelerated aging as measured by DunedinPACE, a new measure of aging that was trained on longitudinal data to detect differences between people in their pace of aging. This association was robust across 4 of the 5 datasets. The exception was one of the 2

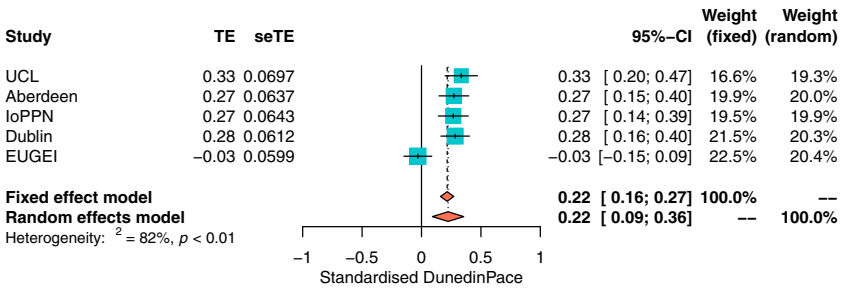

Figure 1. Forest plot of association test results between psychosis and accelerated pace of aging. Pace of aging was measured using the DNA methylation–derived estimate, DunedinPACE (Pace of Aging Calculated from the Epigenome), with higher scores indicating faster aging. DunedinPACE was standardized to have a mean of 0 and an SD of 1 within each dataset, and models were adjusted for age, sex, and DNA methylation–derived estimates of 5 cell types and tobacco smoking behavior. In these analyses, the estimated effect represents the mean difference between psychosis cases and healthy controls in units of SD. TE indicates treatment effect, i.e., the mean difference between cases and controls. EU-GEI, European Network of National Schizophrenia Networks Studying Gene-Environment Interactions; IoPPN, Institute of Psychiatry, Psychology, and Neuroscience; seTE, standard error of TE; UCL, University College London.

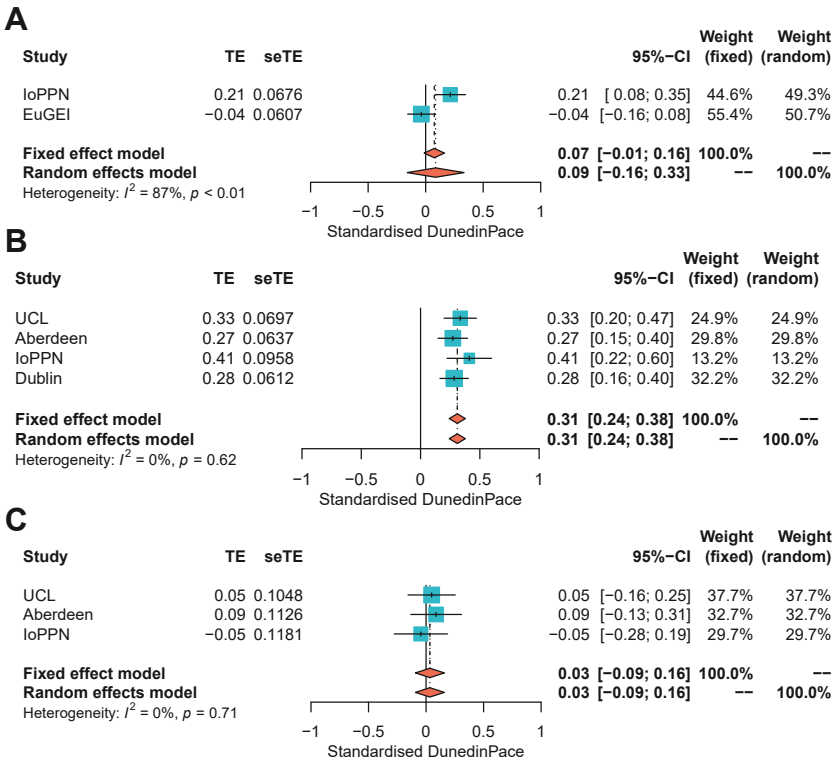

Figure 2. Forest plot of association test results comparing pace of aging in first-episode patients and controls **A)**, schizophrenia cases vs. controls **B)**, and patients with schizophrenia who were prescribed clozapine vs. patients who were not taking clozapine **C)**. Information about drug prescriptions was available for 268 (96 clozapine), 238 (78 clozapine), and 206 (72 clozapine) individuals in the University College London (UCL), Aberdeen, and Institute of Psychiatry, Psychology, and Neuroscience (IoPPN) datasets. Pace of aging was measured using the DNA methylation–derived estimate, DunedinPACE (Pace of Aging Calculated from the Epigenome), with higher scores indicating faster aging. DunedinPACE was standardized to have a mean of 0 and an SD of 1 within each dataset, and models were adjusted for age, sex, and DNA methylation–derived estimates of 5 cell types and tobacco smoking behavior. In these analyses, the estimated effect represents the mean difference between each of the 2 groups compared in units of SD. TE indicates treatment effect, i.e., the mean difference between cases and controls. EU-GEI, European Network of National Schizophrenia Networks Studying Gene-Environment Interactions; seTE, standard error of TE.

datasets in which the epigenetic data came from first-episode cases. This null finding may have emerged because this dataset included the youngest patients in our analysis or because first-episode cases are more heterogeneous and may include some patients who will not convert to schizophrenia, whereas samples of confirmed cases of schizophrenia tend be more severe with more longstanding psychotic illness.

There is an emerging consensus about the relative usefulness of different epigenetic clocks for the study of aging (59). We can speculate about why psychosis/schizophrenia was more robustly related to DunedinPACE than to other DNA methylation measures of aging. The first-generation clocks (the Horvath and Hannum clocks), which stimulated subsequent efforts to measure aging in omics data, are possibly most appropriate for forensic purposes but are less useful as measures of the aging process. Among the second-generation clocks, GrimAge has emerged as a very useful measure of age-related decline. However, GrimAge is highly correlated with tobacco smoking, and it may be that among individuals experiencing schizophrenia, who tend to smoke heavily, its signal is obscured as noted here. DunedinPACE differs from other existing DNA methylation measures of aging in that it is the only one that is trained on actual observed longitudinal decline in multiple organ systems (and it is less correlated with smoking than is GrimAge).

This research benefited from design advantages. The cases in the datasets were well characterized, diagnosed initially in health care settings, and confirmed through standardized clinical assessments. The datasets had DNA methylation data for harmonized measurement of aging. Studying young and middle-aged adults avoided the healthy-survivor bias that characterizes older-adult samples because the life span of individuals with schizophrenia is shorter than the median population life span.

Advantages aside, a limitation of the current study is that comparing cases with controls who were selected to be healthier than the general population (here, free of own and family psychiatric history) sometimes inflates effect sizes (60). In addition, most participants in the 5 datasets are White European, although some ethnic/racial diversity is evident in the IoPPN and EU-GEI samples (Figure S1). Initial evidence suggests that DunedinPACE can yield parallel findings among African American, Asian, and White participants (35,36,61,62). However, to our knowledge, there are no data sets with DNA methylation for non-White ancestry groups in large enough numbers to study schizophrenia. Ancestry groups' experience with severe mental illness differs (63), requiring replication tests of the schizophrenia-aging hypothesis by ancestry. We were also unable to find studies in geriatric psychiatry that have information about schizophrenia and DNA methylation. The participants in the 5 datasets reported here were young to middle-aged adults, and it will be important to extend the research reported here to older age groups. Importantly, DunedinPACE has been shown to be useful as a measure of biological aging among older adults (28). Schizophrenia also co-occurs at high rates with other mental disorders that may be associated with epigenetic aging, which indicates the importance of interpretive caution about whether

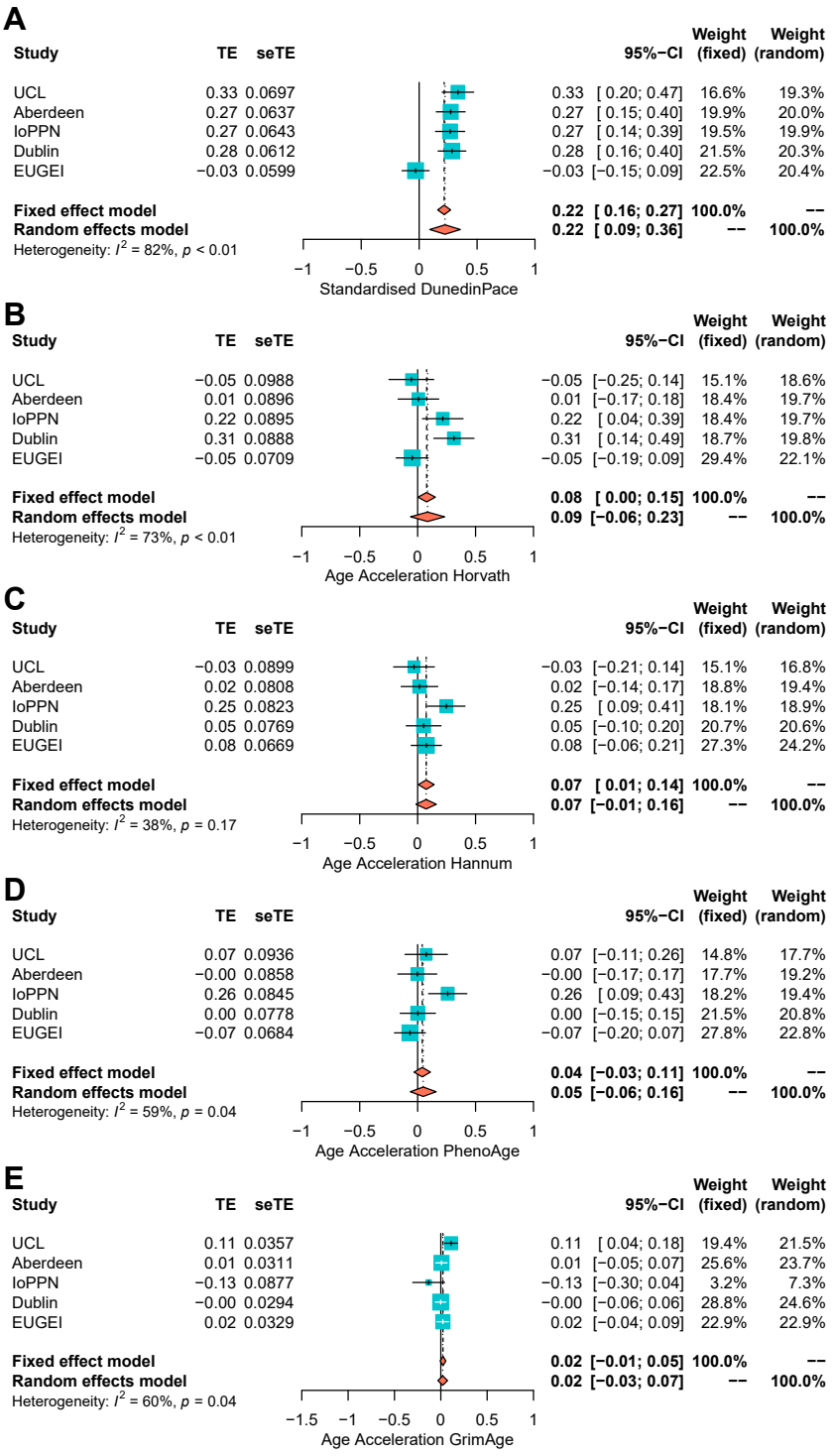

Figure 3. Forest plot of association test results between psychosis and different DNA methylation measures of aging. Shown are forest plots for **A)** DunedinPACE (Pace of Aging Calculated from the Epigenome), followed by **B)** Horvath age acceleration, **C)** Hannum age acceleration, **D)** PhenoAge age acceleration, and **E)** GrimAge age acceleration. In all analyses, the DNA methylation outcome variable was standardized to have a mean of 0 and an SD of 1 within each dataset, and models were adjusted for age, sex, and DNA methylation–derived estimates of 5 cell types and tobacco smoking behavior. In these analyses, the estimated effect represents the mean difference between patients with psychosis and controls in units of SD. TE indicates treatment effect, i.e., the mean difference between cases and controls. EU-GEI, European Network of National Schizophrenia Networks Studying Gene-Environment Interactions; IoPPN, Institute of Psychiatry, Psychology, and Neuroscience; seTE, standard error of TE; UCL, University College London.

schizophrenia is uniquely associated with accelerated aging or whether it is the burden of comorbid psychiatric disease that is consequential (64).

What mechanisms might explain the nding that people living with schizophrenia tend to experience faster whole-body biological aging (65)? Speculations about mechanisms linking

schizophrenia and disease mortality implicate factors thought to accelerate aging, including lack of access to health care, tobacco smoking, and side effects of antipsychotic medications. Whether lacking health care access can explain fast aging in people with schizophrenia is unclear because, on the one hand, the datasets came from nations with free national health care; on the other hand, cost is not the only factor that prevents individuals with schizophrenia from availing themselves of medical care (66). Our analyses suggest that tobacco smoking is only a partial explanation because including smoking as a covariate did not entirely explain the psychosis-DunedinPACE association, although it did explain initial associations between schizophrenia and GrimAge. Our analyses also raise questions about a primary role for antipsychotics in accelerating aging because, among schizophrenia cases, patients who were prescribed clozapine did not differ in their pace of aging from patients who were not taking clozapine, which is prescribed after other drugs have been tried. This is consistent with the nding in a longitudinal cohort that thought disorders predicted accelerated pace of aging even among unmedicated individuals (67). Initial research into the epigenetic effects of antipsychotic medication using cell-culture models also has not shown consistent acceleration or deceleration effects on DNA methylation-based clock age estimators (68). Moreover, younger death from diseases in individuals with schizophrenia was reported before the advent of antipsychotics (8). The side effects of psychotropic medication are known to include weight gain and metabolic disturbances (69,70), but it is not clear whether they account for the association between psychosis and accelerated aging. Nevertheless, the datasets studied here were not designed to test the possibility that long-term exposure to antipsychotics may have iatrogenic effects, including accelerated aging. That possibility needs to be evaluated further.

Some evidence suggests that schizophrenia and accelerated aging may share the same causes (8). For example, childhood maltreatment history predicts both schizophrenia (71) and faster DunedinPACE (i.e., faster pace of aging as calculated from the epigenome) (28,64). Long-term cannabis use also predicts both schizophrenia (72) and faster DunedinPACE (73). Schizophrenia and accelerated aging may share the same genetic causation as suggested by ndings of shared genetics between schizophrenia and a variety of age-related diseases (74–76). The hypothesis that schizophrenia and age acceleration coincide because they share causes requires more study.

People with schizophrenia are known to die prematurely, not only from suicide but also from prematurely contracting a variety of aging-related diseases (77). The current study, which showed a pronounced difference in the pace of aging between patients with schizophrenia and controls, raises the possibility that part of what brings early mortality is that schizophrenia is accompanied by acceleration in whole-body biological aging toward disease, an acceleration that is measurable by the thirties, years before the onset of age-related diseases. This nding of an association between schizophrenia and whole-body biological aging is consistent with ndings that suggest an association between schizophrenia and older brain-predicted age (78). This could help explain schizophrenia s wide-ranging associations with different physical diseases, including metabolic, cardiovascular, and respiratory diseases and dementia. Needed longitudinal research can now begin to test whether fast DunedinPACE mediates the association between diagnosed schizophrenia and disease mortality.

If DunedinPACE mediates the association between schizophrenia and disease mortality, this nding would further raise the hypothesis that successful treatments for psychosis may also slow aging or conversely that successful treatments intended to slow aging may also improve the health of patients with psychosis (79–81). Reports are emerging that DunedinPACE can be slowed by caloric restriction (82), adopting a healthy diet and reducing tobacco use (83), and reducing stress (84). Testing hypotheses of treatment-induced change will require that randomized clinical trials incorporate measures of accelerated aging into their protocols.

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