Schizophrenia Bulletin Open
https://doi.org/10.1093/schizbullopen/sgac030

Dysmaturational Longitudinal Epigenetic Aging During Transition to Psychosis

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Psychosis frequently occurs during adolescence and young adulthood, possibly as a result of gene-environment interactions, mediated by epigenetic mechanisms such as DNA methylation. Methylation patterns can be leveraged to predict epigenetic age in order to identify anomalies in aging trajectories that may be associated with the emergence of psychosis. Thus, epigenetic age may provide a measurable surrogate of psychotic risk or psychosis' emergence, and shed light on the neurodevelopmental model of psychosis. In this study, we present the first longitudinal analysis of epigenetic age trajectory during conversion to psychosis in a population at ultra-high-risk, with available genome-wide methylation DNA at two time points, at baseline and after one year of follow-up ($N = 38 \times 2$). After predicting epigenetic age, we computed epigenetic age gap as the cross-sectional difference between real age and predicted age, and (longitudinal) epigenetic age acceleration as the derivative of predicted age with respect to time. At baseline, future converters were 2.7 years younger than nonconverters and this difference disappeared at follow-up, when some converted to psychosis. This is because during conversion to psychosis, the epigenetic age of converters accelerated by 2.8 years/year compared to nonconverters. This acceleration was robust with a strictly positive 95% confidence interval, and held its significance after adjustment for age, sex, and cannabis intake. The methylation sites most associated with aging were on genes also linked with schizophrenia and neurodevelopmental disorders. This accelerated age trajectory, following a previous deceleration, may therefore reflect dysmaturational processes.

Key words: ultra-high-risk/epigenetic clocks/methylation/neurodevelopment/dysmaturation

Introduction

Abnormal neurodevelopment and early neurodegeneration are two different models that have been proposed to explain the emergence of psychosis.[1,2] On the one hand, schizophrenia is associated with early age-related conditions, metabolic dysfunctions, and cardiovascular diseases,[3] which contribute to the persistent excess in life-years loss, despite improvement in disease-specific care.[4,5] These risks are only partially explained by illness duration, antipsychotic side-effects, or an unhealthy diet,[6] suggesting that they may have a component intrinsic to psychosis. Thus, an increase in age-related morbidity and mortality was observed early during the course of schizophrenia.[7,8] On the other hand, dysmaturation hypotheses are supported by evidence that gene variation may affect longitudinal brain trajectories in psychosis,[9] and that adolescence and early adulthood, time frames with the highest incidence of psychosis,[10] are also critical periods of interaction between genetic vulnerability, environmental stress, puberty, and hormonal factors.[1,11,12] Therefore, whether dysmaturational or degenerative, understanding age trajectory may contribute to a better characterization of disease course, improved prevention, and early healthcare.[2,13] Among subjects at ultra-high-risk of psychosis (UHR), 15% will experience a first episode of psychosis in the next year, reaching 25% at three years ("converters"), while the rest will remain at-risk or achieve symptomatic remission ("nonconverters"),[14] a differential outcome that is poorly understood. In this context, anomalies in biological age trajectories may also constitute a proxy of psychotic risk.

Biological age can be measured peripherally, in the blood, using epigenetic clocks that predict age or age-related outcomes based on DNA methylation (mDNA) patterns[15] – these are patterns that reflect gene-environment interactions at genetic level through modulation of gene expression, which may be crucial to the emergence of disease.[16] Biological age prediction can provide two different pieces of information. The first, "*age gap*", is the difference between biologically predicted age

and chronological age. It results from cross-sectional studies at one time point and translates an age acceleration having already occurred. The second, "*age acceleration*", is the variation of biologically predicted age across time. It can only be provided by longitudinal studies and it describes an age acceleration or deceleration occurring *during* the time frame of observation (figure 1).[17] In schizophrenia, epigenetic age studies provided contrasted results, depending on the type of epigenetic clock and the outcome under study.[15] Mortality-related methylation clocks showed age gaps increases up to 5 years in individuals with schizophrenia, and mDNA-based predictors of telomere lengths, which decrease with replication cycles, found shorter sizes, also suggesting an acceleration of aging in schizophrenia.[15] Conversely, mDNA predictors of lifetime mitotic divisions identified decreases in patients' tissue, while the prediction of epigenetic age per se, using Horvath's epigenetic clock,[18] did not find any difference between the groups.[15] A large-scale epigenetic-based study similarly found no evidence of biological age difference between schizophrenia and controls.[35] Nevertheless, another recent large-scale study demonstrated that, both in whole-blood and in brain tissue, methylation-based age gaps were decreased in schizophrenia compared to controls.[19]

The nature of cross-sectional designs could provide an explanation for these conflicting results: longitudinal designs may catch an individual biological age variation that may not be constant across time and therefore lead to varying observations in case-control experiments depending on the individual's time point.[17] In particular, longitudinal studies assessing the relevance of disrupted age trajectories during the emergence of psychosis are lacking,[15] despite arguments in favour of age-related pathways' dysregulation at early stages—eg, shorter leukocyte telomere length in UHR subjects,[20] or longitudinal methylomic and transcriptomic changes in genes from the redox metabolism that have been associated both with age[21] and the emergence of psychosis.[22,23]

Here, we present the first longitudinal study of epigenetic age trajectory during conversion to psychosis in an UHR population, with available genome-wide mDNA data at two timepoints, at baseline and after one year of follow-up ($N = 38 \times 2$). Using the predicted epigenetic age, we compared epigenetic age gaps at baseline and follow-up, as well as epigenetic age acceleration over time, between converters and nonconverters to psychosis. We hypothesized that there would be a longitudinal methylomic age acceleration during the emergence of the symptoms, regardless of baseline age gaps values.

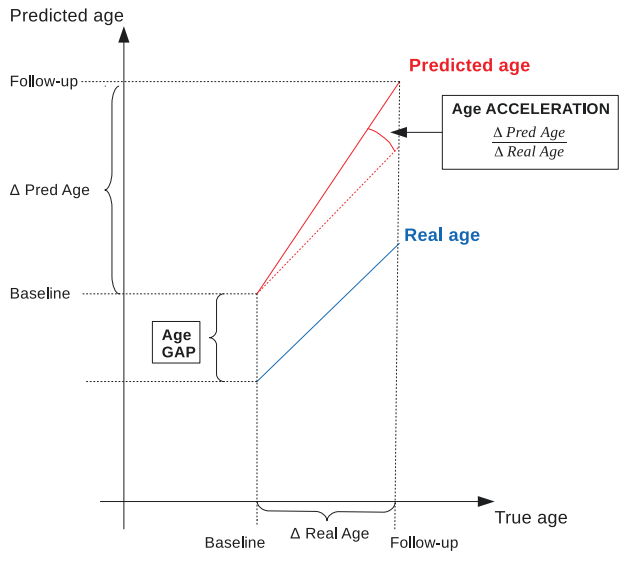

Fig. 1. Predicted age gap and age acceleration. Δ Real Age is the difference between age at follow-up and age at baseline. Δ Pred Age is the difference between predicted age at follow-up and predicted age at baseline. Age acceleration is Δ Pred Age divided by Δ Real Age.

Methods

Participants

Help-seeking adolescents and young adults have been screened in the prospective multicenter cohort ICAAR (*Influence du Cannabis sur l'émergence de symptômes psychopathologiques des Adolescents et jeunes Adultes présentant un état mental à Risque*).[24] Individuals were assessed with the CAARMS[25] in its French-translated version.[26] After baseline assessment, a consensus meeting for best estimated diagnosis was held, and help-seekers were classified as at-risk for psychosis stage IA or stage IB according to the staging model distinction.[27] Stage IA included patients with mild or nonspecific symptoms of psychosis or severe mood disorder, and mild functional change. Stage IB included patients with moderate subthreshold symptoms and moderate functional change. Inclusion criteria were an age less than 30 years old, alterations in global functioning (Social and Occupational Functioning Assessment Scale score < 70) during the past year, which were associated with psychiatric symptoms and/or subjective cognitive complaints. Exclusion criteria included manifest symptoms of psychosis (fulfilling DSM-IV criteria), or other established psychiatric diagnoses (pervasive developmental disorder, bipolar disorder, obsessive compulsive disorder), serious or nonstabilized somatic and neurological disorders, head injury, and IQ below 70. Psychotic conversion was characterized using the CAARMS-defined psychosis onset threshold (ie, supra-threshold psychotic symptoms—thought content, perceptual abnormalities, and/or disorganized speech—present for more than one week). Individuals who reached the threshold during the one-year follow-up were considered converters and individuals who recovered or displayed persistent subthreshold symptoms were called nonconverters. For each subject, the following clinical data were

recorded: sex, age, clinical symptom scales for depression (MADRS), psychotic symptoms (PANSS), social functioning (SOFAS), current antipsychotic treatment summarized by the chlorpromazine equivalent doses, alcohol, cannabis, and tobacco intakes in the last month. The study was approved by the institutional ethics committees (Comité de protection des personnes, Ile-de-France III, Paris, France for ICAAR and Comité de protection des personnes, Ile-de-France IV, Paris, France for PsyDev). Written informed consent was obtained from all participants or their legal representatives.

Methylation DNA and Epigenetic Age Prediction

Genome-wide DNA methylation was assessed in the peripheral whole blood of 38 UHR (15 converters vs 23 nonconverters), from one site, at two timepoints. The Illumina Infinium HumanMethylation450 BeadChip (Illumina, San Diego, CA, USA) was used as previously reported.[22] Preprocessing steps for annotation, normalization, and quality assessment were done in R version 3.4.4 (2018-03-15) using the Minfi package.[28] Horvath's DNA age methylation calculator (https://dnamage.genetics.ucla.edu/home) has already been well-validated on large independent datasets.[18] We directly applied it to predict epigenetic age at two time points, at baseline and after one year of follow-up. Epigenetic age gaps at baseline and at follow-up were computed as the difference between methylation-based predicted age and chronological age. Epigenetic age acceleration was computed as the derivative of epigenetic age across time (ie, the slope, or tangent of the angle: the difference in epigenetic age between the two time points divided by the difference in chronological age between these timepoints). A null acceleration would therefore be equivalent to a value of one.

Statistical Analysis

Univariate analysis of the demographic and clinical data was done with a Chi²-test for categorical variables, and the Mann–Whitney–Wilcoxon test for quantitative variables. Confidence intervals at 95% (95%CI) were computed by bootstrapping, where the variance of means from each group was estimated by random sampling with replacement, to avoid any inference on the statistical distribution of the population. Lower and upper confidence bounds were picked as 2.5th and 97.5th percentiles of the bootstrap distribution. To test whether conversion to psychosis would lead to an increase in either age gap or age acceleration, we regressed age gap, or acceleration, on status (converter or nonconverter) and we corrected for a number of possible confounding variables, as follows. First, it has been shown that age prediction studies need to adjust for chronological age because any imperfect correlation between chronological and predicted age can lead to regression towards the mean,[28] resulting in an overestimation of age gap for younger subjects, and an underestimation for older subjects, regardless of cohort size or age distribution.[30,31] Thus, it is recommended to add chronological age effect as a covariate in the final age gap regression on the variables of interest.[30] Second, DNA methylation patterns are known to be affected by cannabis use,[32] psychotropic medication,[33] and tobacco use.[34] Therefore, we tested models including increasingly more covariates, from "*age gap (or acceleration) ~ conversion + sex*" to "*age gap (or acceleration) ~ conversion + sex + baseline age + cannabis + medication + tobacco*". As the Jarque-Bera test showed that residuals were not normally distributed, a quantile regression was used to model the median of age gap or acceleration. One-sided t-tests were used as the hypothesis was that conversion is associated with a positive epigenetic age acceleration.

Results

Demographic and Clinical Characteristics of the UHR Population

Baseline demographic and clinical characteristics are available in table 1. Longitudinally, patients were followed for 10.8 months on average, and there was no difference in follow-up time between converters and nonconverters. Converters were younger in age, had higher severity on the PANSS, and smoked more cannabis and tobacco. The sex ratio of converters was biased toward males. Across time, future converters showed an increase in negative symptoms compared to nonconverters.

Age Prediction

Across the whole dataset of 76 samples, the Horvath epigenetic clock provided methylomic based predicted ages that showed a correlation with chronological age of $r = 77\%$ (p = 4e-16), with a mean absolute error of 3.3 years, and a root mean squared error of 4.1 years (figure 2).

Baseline and Follow-up Epigenetic Age Gaps

At baseline, epigenetic age gap was lower in future converters (median = 0.91, std = 3.22, 95%CI = [−1.09, 4.51]) compared to nonconverters (median = 3.64, std = 3.15, 95%CI = [0.71, 5.24]), with U = 116.0, and $P = .047$ (figure 3A). In median, future converters were 2.7 years younger than nonconverters. When adding covariates to the model, this association was not significant anymore. Notably, in the full model, baseline epigenetic age gap was positively associated with sex ($P = .045$), baseline age ($P = .004$), borderline with cannabis ($P = .063$), but not with tobacco ($P = .239$). At follow-up, there was no significant difference in epigenetic age gap between future converters (median = 2.14, std = 3.4, 95%CI = [1.15, 5.16]) and nonconverters (median = 2.46, std = 3.27, 95%CI = [0.82, 4.43]), with U = 163.0, and p = 0.39 (figure 3B).

Table 1. Demographic and Clinical Characteristics of the Longitudinal Methylation Dataset

Measure	UHR Longitudinal Cohort		Mann–Whitney–Wilcoxon Test X^2 for Proportions	
	Converters (15)	Nonconverters (23)	Test Statistic	*P*-value
Demographics				
Age at baseline	20.5 ± 2.5	23.0 ± 4.3	115.5	.09
At follow-up	21.4 ± 2.6	23.9 ± 4.3	111.5	.07
Follow-up time (year)	0.9 ± 0.6	1.0 ± 0.5	100.0	.31
Sex (F/M)	4/11	12/11	8.24	**.004**
Symptoms at baseline				
MADRS	20.2 ± 8.2	28.2 ± 12.8	126.0	.08
PANSS total	77.0 ± 15.7	71.2 ± 13.5	117.5	.05
Positive	19.2 ± 5.6	12.7 ± 4.5	108.5	**.03**
Negative	18.0 ± 6.5	16.8 ± 6.5	118.0	.05
Desorganisation	9.2 ± 2.3	5.0 ± 1.7	107.0	**.03**
SOFAS	50.2 ± 7.5	45.2 ± 9.6	112.5	**.04**
Treatment				
Antipsychotic use (%)	27 (4/15)	17 (4/23)	2.27	.13
Chlorpromazine equivalent	124.5 ± 300.9	17.3 ± 45.3	151.5	.20
Substance use (last month) at baseline (% and true ratios in brackets)				
Alcohol	13.3 (2/15)	21.7 (5/23)	1.69	.19
Tobacco	20 (3/15)	8.7 (2/23)	4.45	**.03**
Cannabis	40 (6/15)	13 (3/23)	13.7	**.0004**
Longitudinal variation in clinical scales				
MADRS	−8.5 ± 10.9	−9.7 ± 10.7	121.0	.28
PANSS total	0.6 ± 32.9	−7.6 ± 17.4	92.0	.06
Positive	−0.6 ± 10.0	−0.7 ± 5.4	126.5	.35
Negative	4.0 ± 8.7	−2.0 ± 6.5	72.0	**.01**
Desorganisation	−0.4 ± 6.8	−0.6 ± 2.2	135.0	.46
SOFAS	4.7 ± 14.7	11.0 ± 15.6	104.5	.13
Cannabis (variation between semi-quantitative levels)	−0.2 ± 1.1	0.0 ± 0.7	33.0	.42

Note: PANSS, Positive And Negative Syndrome Scale; SOFAS, Social and Occupational Functioning Assessment Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

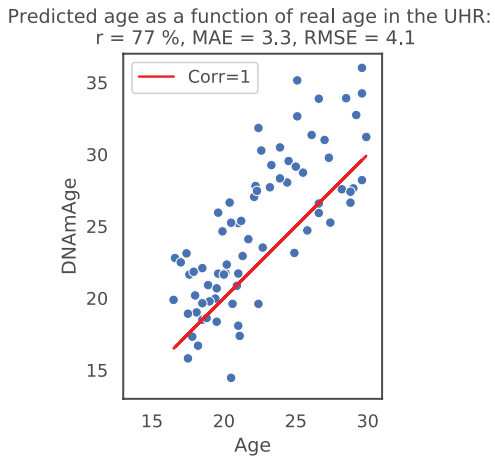

Fig. 2. Overall performance of the age predictor in the UHR population, regardless of status; *r* = Pearson's correlation, MAE = mean absolute error, RMSE = root mean squared error.

Longitudinal Epigenetic Age Acceleration

From baseline to follow-up, epigenetic age was significantly accelerated in future converters (median = 2.53, std = 19.3, 95%CI = [1.05, 5.18]) compared to nonconverters (median = −0.29, std = 4.55, 95%CI = [−1.21, 1.91]), with U = 108.0, *P* = .014. Future converters accelerated their aging with a median of 2.82 more years per year compared to nonconverters. The 95%CI of nonconverters' age acceleration did not exclude a null acceleration (figure 4). Epigenetic age acceleration remained significantly higher in future converters compared to nonconverters after adding baseline age, sex, and cannabis as covariates. When using medication as a covariate, we found no effect on age acceleration, while the association between conversion and acceleration was close to significance. When adding cannabis, medication, and tobacco use, the association was not significant anymore (table 2). None of the covariates significantly explained age acceleration in any model.

We tested all 353 CpGs sites used for epigenetic age prediction to see which showed a variation in methylation profile across time that correlated with longitudinal age acceleration in the UHR population. We found that 94% of CpG methylation variations (331/353) were negatively correlated with age acceleration. After Bonferroni correction for multiple testing—with a conservative adjusted p threshold of 0.00014—six CpG sites showed decreases

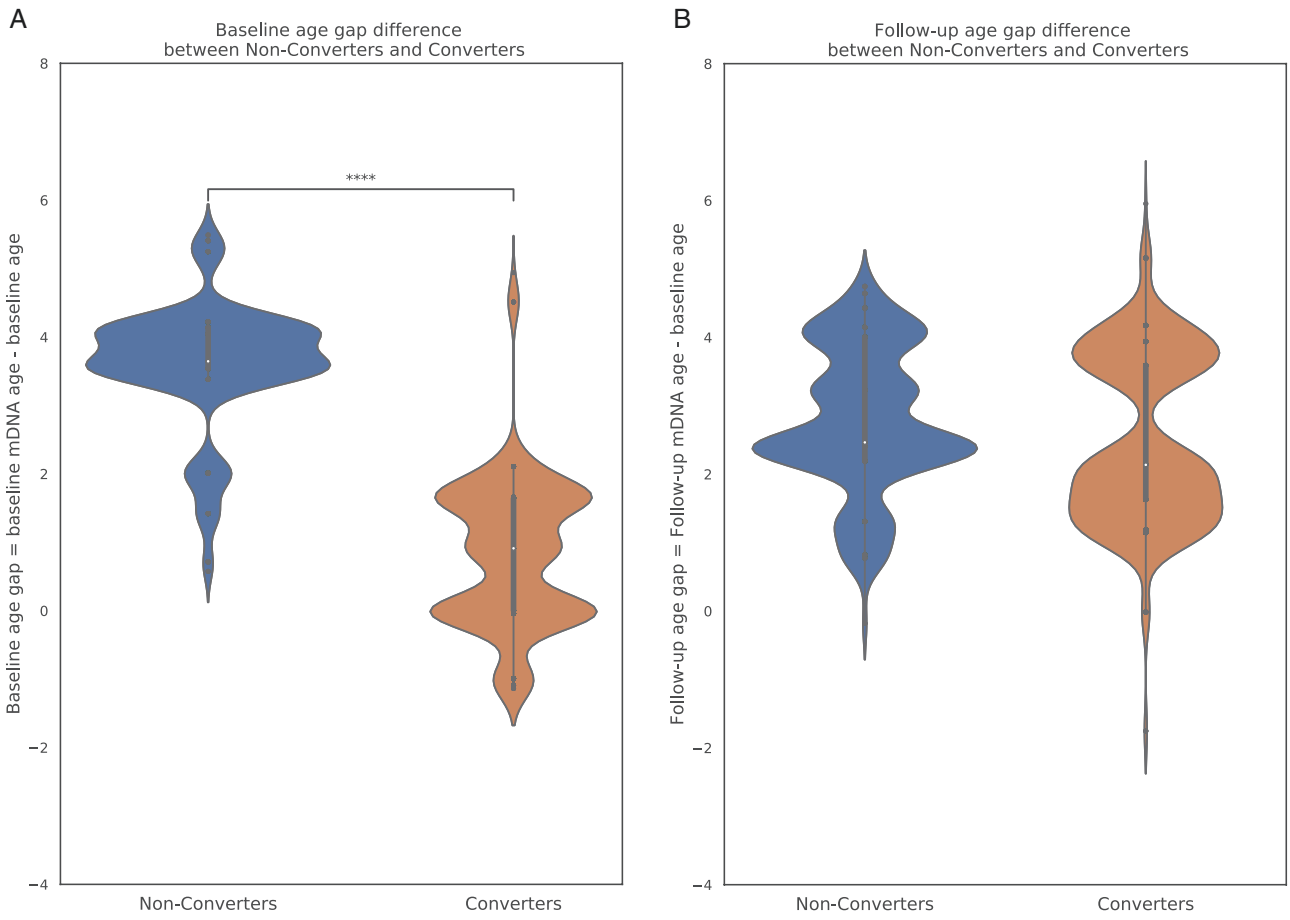

Fig. 3. Epigenetic age gaps at baseline (A) and follow-up (B).

in methylation significantly correlated with age acceleration: cg14175438 (ρ = −0.61, p = 4e-5), cg15381769 (ρ = −0.59, p = 0.9e-4), cg16579101 (ρ = −0.62, p = 3e-5), cg22637507 (ρ = −0.58, p = 1e-4), cg25683012 (ρ = −0.61, p = 6e-5), cg26162695 (ρ = −0.57, p = 1e-4). The genes possibly affected by this methylation were *OR6C1, IFFO1, ARHGAP44, LAMA2*, and *TSPAN12*.

Discussion

In this work, we presented the first longitudinal analysis of epigenetic age trajectory during the emergence of psychosis in a prospective UHR cohort. We predicted baseline and follow-up epigenetic age using the Horvath epigenetic clock on 38 UHR subjects with longitudinal methylation data available at two time points. Our cross-sectional results replicated those of the two most recent large-scale cross-sectional predictions of epigenetic age, while offering a possible explanation for their conflicting results. At baseline, future converters were epigenetically younger than nonconverters, as it was also reported by Wu and colleagues in subjects with psychosis, using the same Horvath clock.[18] At follow-up, once some subjects converted to psychosis, there was no epigenetic gap difference anymore between actual converters and nonconverters, which is in line with the other large-scale study that compared patients with psychosis and controls, also with the Horvath clock.[35] This demonstrates that epigenetic aging is dynamic and may vary across time points, depending on clinical stage or environmental factors, as previously described with regard to longitudinal brain age variation.[17] Thus, we found that although converters were epigenetically younger at baseline, they showed an accelerated methylomic aging of 2.82 years/year during the conversion time frame, while nonconverters maintained a constant aging, without acceleration. This association remained significant after adjustment for age, sex, and cannabis use, but not when medication and tobacco were introduced as covariates. Methylomic age acceleration was largely correlated with longitudinal hypomethylation among most of the 353 CpGs used for age prediction. This is in line with the fact that age- or environmental stressor-related effects are known to mainly cause global hypomethylation, with the exception of CpG islands that may show hypermethylation.[36] The six CpG sites whose methylation variation significantly correlated with age acceleration, after correction for multiple testing, were located in *OR6C1* (olfactory receptor), *IFFO1* (intermediate filament family orphan 1), *ARHGAP44* (rho GTPase activating protein 44), *LAMA2* (laminin), and *TSPAN12*

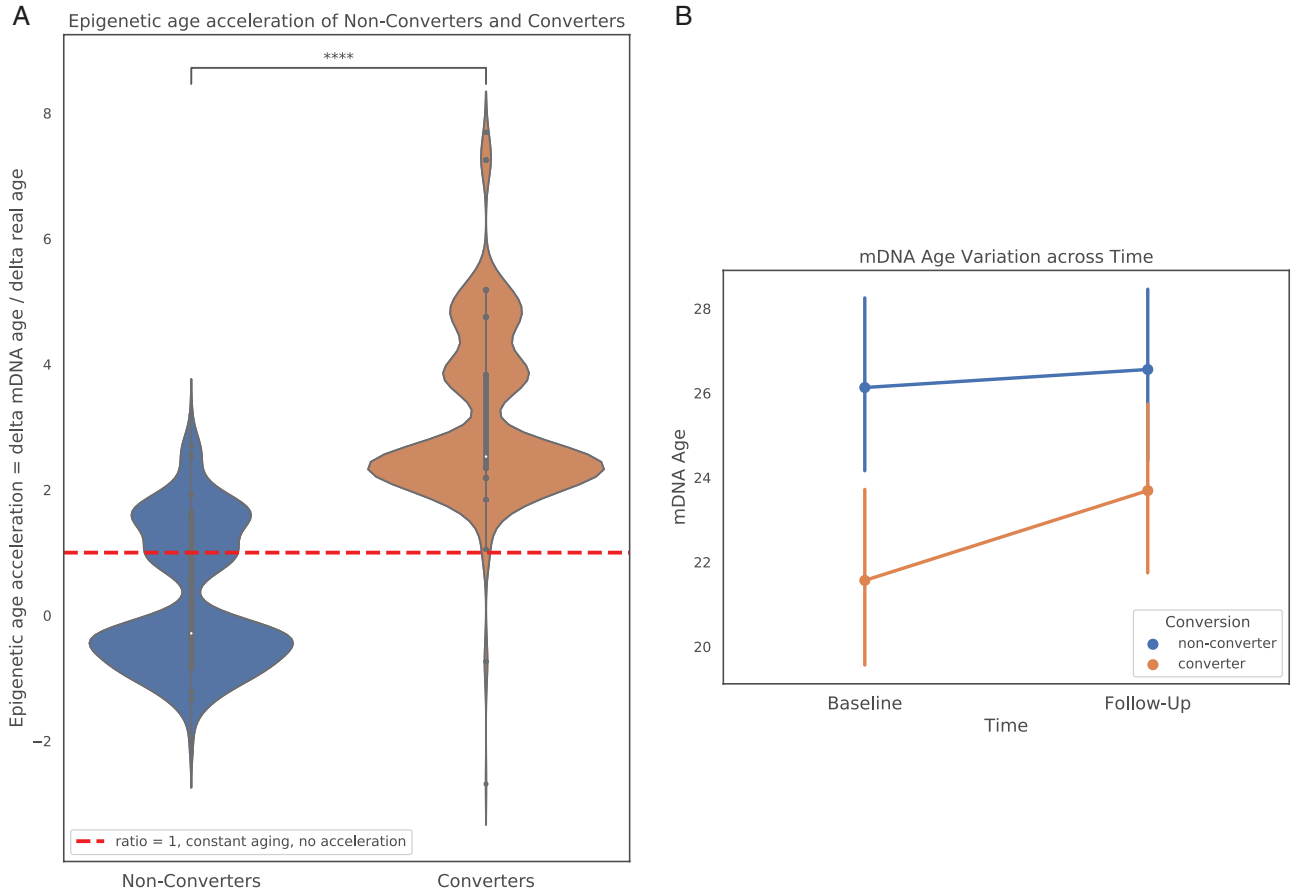

Fig. 4. Epigenetic age acceleration as a comparison of ratios (A) and as a mDNA variation between time points in converters and nonconverters (B); the dotted line indicates a ratio of 1, meaning constant aging, with no acceleration.

(tetraspanin 12) genes. According to the GeneCards database, IFFO1 participates to DNA repair, ARHGAP44 may be involved in dendritic spine formation and synaptic plasticity (by similarity), LAMA2 may mediate cell migration and organization into tissues during embryonic development, and TSPAN12 regulates cell surface receptor signal transduction, and membrane proteinases. Notably, LAMA2 was found to be among genes recurrently affected by de novo mutations associated with schizophrenia,[37] while *ARHGAP44* is part of a family of genes coding for GTPase activating proteins, where copy number variants have been found more frequently associated with schizophrenia and neurodevelopmental disorders, as well as reduced spine density in the medial prefrontal cortex of animal models.[38] While anomalies in the methylation of these genes have been found to contribute to aging and age prediction,[18] the fact that some of the same genes are also linked with schizophrenia may strengthen the idea of an association between this disease and intrinsic dysfunctions in age trajectories.

Several considerations need to be taken into account. First, the longitudinal design allowed the detection of significant differences despite a small sample size. Indeed, longitudinal settings are more powerful than cross-sectional ones as they adjust for any individual variation unrelated to disease because each subject is its own control.[39] Second, in order to predict epigenetic age, we applied the well-validated mDNA-based Horvath clock,[18] because it has been shown to be the most performant for chronological age prediction in young subjects,[40] and also the less prone to error. In our work, we found a correlation of 77% between chronological and predicted ages, with a mean absolute error of 3.3 years. Along these lines, Wu and colleagues found that the Horvath clock predicted age with a similar performance (error of 3.7 years) and a higher correlation of 96% (the fact that we obtained a lower correlation despite the same prediction performance is due to the younger age distribution of our cohort—Supplementary). Conversely, they showed that other clocks such as Hannum's and Levine's were less performant, with greater errors (8.3 and 11 years respectively).[19] Such large positive errors are also exacerbated in younger cohorts due to the poor availability of mDNA datasets of young subjects in the various epigenetic learning sets. The Hannum clock is based on 656 subjects aged 19 to 101,[41] and the Levine clock is built on more than 9000 samples, but from 21 to 100.[42] Therefore, any use on young subjects like the ones in this UHR cohort,

Table 2. Association Between Conversion to Psychosis and Epigenetic Age Acceleration, With Quantile Regression Models Including an Increasing Number of Covariates

Model (EAA = Epigenetic Age acceleration)	β Parameter Conversion	T-value Conversion	One-sided *P*-value Conversion	One-sided 95%CI Conversion
EAA ~ conversion + sex	3.6	2.34	0.012	>0.99
EAA ~ conversion + sex + baseline age	3.1	1.73	0.046	>0.07
EAA ~ conversion + sex + baseline age + cannabis	3.3	1.74	0.046	>0.09
EAA ~ conversion + sex + baseline age + medication	3.0	1.68	0.051	>−0.024
EAA ~ conversion + sex + baseline age + cannabis + medication	2.4	1.2	0.11	>−0.84
EAA ~ conversion + sex + baseline age + cannabis + medication + tobacco	2.1	1.1	0.14	>−1.19

on the extreme lower tail of the learning algorithm's distribution, will necessarily lead to regression to the mean effects with extreme overestimations of the predicted age.[29–31] To our knowledge, only the Horvath predictor accounted for adolescence and young adulthood periods by including samples of subjects starting from birth, and adjusting for the nonlinear aging trajectories occurring around 20.[18] Nevertheless, to account for a possible regression to the mean also related to the nominal age difference between converters and nonconverters, and following recent benchmark recommendations,[30] we also tested models with chronological age as a covariate, which did not change the association between disease and age acceleration.

Third, the significance of the age acceleration that we reported is robust, with a bootstrapped 95% confidence interval excluding the null acceleration. Moreover, we took advantage of a deeply phenotyped cohort in order to adjust for known confounders of methylation patterns—cannabis, tobacco, and medication. Our iterative addition of covariates to this model showed that conversion to psychosis may lead to increased epigenetic age acceleration independently of age, sex, and cannabis intake, but not of medication and tobacco use. However, these last two measures are semi-quantitative and their use as covariates may also lead to overcorrection of a relevant variance, especially as there is high collinearity between tobacco and cannabis, and between status and medication.

Finally, result interpretation is limited by several points. Converters had a higher male/female ratio, and males are expected to be epigenetically older than females, across the lifespan.[43] Although we included sex as a covariate in the estimation of association between epigenetic age and conversion, we cannot fully exclude a possible bias in mDNA measures. Converters are also slightly—although not significantly—younger than nonconverters. Having also adjusted for age as a covariate, this raises nevertheless the question of whether the observed difference in age acceleration is truly associated with the emergence of psychosis or is related to normal maturational aging, which is physiologically more accelerated at younger ages.[18,44] Longitudinal studies with matched chronological age distributions between groups could answer this question. Lastly, our interpretation of aging is intrinsically limited by the little insight we have on the underlying mechanisms. Beyond methylation, other epigenetic mechanisms such as microRNAs may be relevant and need to be considered in psychosis.[16] It is also unclear whether age acceleration translates a pathologic process at the core of conversion to psychosis or is rather an adaptive mechanism of epigenome maintenance under environmental pressure.[40,44] This will have implications on how age acceleration could be clinically relevant, either as a biomarker of risk or as a target of treatment itself.

In summary, our results support a neurodevelopmental model of the emergence of psychosis. This study of longitudinal epigenetic aging, which identified both a decreased epigenetic age gap at baseline, in favor of previous epigenetic age deceleration,[19] and an epigenetic age acceleration contemporary to psychosis' emergence, may underpin the hypothesis of a dysmaturational process, different from constant progressive premature aging. If replicated in larger studies, age acceleration could constitute a measurable surrogate dynamic biomarker of risk of psychosis, and exploration of its underlying pathway may uncover new targets for early intervention.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

Funding

This work was supported by Fondation pour la Recherche Médicale (FDM201806006059 to AI), Fondation Bettencourt-Schueller (CCA-INSERM-Bettencourt to BC), the French government's "Investissements d'Avenir" programme "Projet Psycare" (ANR-18-RHUS-0014), the French Ministry grant PHRC AOM07-118 (for the ICAAR cohort), Institut National de la Santé et de la Recherche Médicale (INSERM), Université Paris Cité. (recurrent funding).

Acknowledgments

We would like to thank all the patients and parents who participated in the ICAAR study, the staff from the C'JAAD team and the staff from the Clinical Evaluation and Research Center at the Service Hospitalo-Universitaire, Centre Hospitalier Sainte-Anne. We would like to thank the collaborators of the ICAAR Study Group: Isabelle Amado, Julie Bourgin, Claire Daban Huard, Célia Jantac Mam-Lam-Fook, Marion Plaze, Fabrice Rivollier. We are also grateful to the GHU Paris Psychiatrie et Neurosciences, which promoted the study. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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