Archival Report

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Combining Clinical With Cognitive or Magnetic Resonance Imaging Data for Predicting Transition to Psychosis in Ultra High-Risk Patients: Data From the PACE 400 Cohort

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ABSTRACT

BACKGROUND: Multimodal modeling that combines biological and clinical data shows promise in predicting transition to psychosis in individuals who are at ultra-high risk. Individuals who transition to psychosis are known to have deficits at baseline in cognitive function and reductions in gray matter volume in multiple brain regions identified by magnetic resonance imaging.

METHODS: In this study, we used Cox proportional hazards regression models to assess the additive predictive value of each modality—cognition, cortical structure information, and the neuroanatomical measure of brain age gap—to a previously developed clinical model using functioning and duration of symptoms prior to service entry as predictors in the Personal Assessment and Crisis Evaluation (PACE) 400 cohort. The PACE 400 study is a well-characterized cohort of Australian youths who were identified as ultra-high risk of transitioning to psychosis using the Comprehensive Assessment of At Risk Mental States (CAARMS) and followed for up to 18 years; it contains clinical data (from N = 416 participants), cognitive data (n = 213), and magnetic resonance imaging cortical parameters extracted using FreeSurfer (n = 231).

RESULTS: The results showed that neuroimaging, brain age gap, and cognition added marginal predictive information to the previously developed clinical model (fraction of new information: neuroimaging 0%–12%, brain age gap 7%, cognition 0%–16%).

CONCLUSIONS: In summary, adding a second modality to a clinical risk model predicting the onset of a psychotic disorder in the PACE 400 cohort showed little improvement in the fit of the model for long-term prediction of transition to psychosis.

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The development of criteria for ultra-high risk (UHR) of psychosis has facilitated early intervention strategies to promote better clinical outcomes (1). Although there is meta-analytic evidence that 25% of individuals at UHR for psychosis transition to first-episode psychosis over a 3-year period (2), we are currently unable to identify the level of risk at the individual level. Being able to do this would enable individualized treatment strategies to be developed using currently available treatments and would also enable efficient stratification of individuals at UHR in clinical trials of new treatments.

To date, the majority of approaches that have attempted to generate individualized prediction models have used either traditional multivariate techniques such as Cox proportional hazards (3–6) and logistic regression (7,8) or machine learning models such as support vector machines (9–11) and greedy algorithms (12). Recently, prediction models that combine multiple domains such as clinical, structural magnetic resonance imaging (MRI), cognition, genetic markers, and blood markers have been shown to improve psychosis prediction accuracy in UHR cohorts, e.g., as demonstrated by the Personalised Prognostic Tools for Early Psychosis Management (PRONIA) consortium in recent studies using multimodal, multisite machine learning models (11,13). Such multimodal models can provide more important information regarding the value of more expensive and complex assessment workflows including genomic testing and MRI than structured clinical and cognitive assessments (14,15). To drive the implementation of prediction models in practice, there is a need to understand the benefit of including complex assessments because a low number of predictors or modalities, in particular noninvasive modalities, lowers the difficulty of translation into clinical practice and should be included as objective during the

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development of prediction models in addition to a high predictive accuracy. Here, we validated the new information introduced by new predictors in a nested Cox regression model by determining the fraction of new information added to the total predictive information over an extended follow-up period during which we investigated the relevance of adding complex modalities.

Clinical variables that are known to predict transition to psychosis in UHR cohorts include long duration of symptoms prior to presentation to clinical services (16,17), severity of positive (18,19) and negative psychotic symptoms (20,21), and poor functioning and quality of life (22,23). Cognition is impaired across domains in individuals at UHR for psychosis and is a key prognostic biomarker of transition to first-episode psychosis (FEP) (24). Neuroimaging studies have found the surface area in the rostral anterior cingulate, lateral and medial prefrontal regions, parahippocampal gyrus (25), the mean anterior genu thickness (26), and the cortical thinning rate (27) to be predictive of transition to psychosis. One relatively new imaging concept, brain age gap, shows potential for prediction for transition to FEP (28). MRI scans can be used to estimate an individual's brain age by using prediction models that were trained on normative population data (29). Brain age gap refers to the difference between the estimate of an individual's brain age and the individual's chronological age (30). A positive brain age gap indicates an older brain compared to the person's chronological age whereas a negative brain age gap suggests a younger brain. Brain age gap has been part of an increasing number of studies over the past decade which have shown that higher brain age gap scores are associated with cognitive impairment and with schizophrenia or bipolar disorder (11,31,32–34).

In the current analysis, we investigated the potential benefit of using a multimodal model compared to using a clinical risk model alone to estimate the transition hazard in individuals at UHR for psychosis using the PACE (Personal Assessment and Crisis Evaluation) 400 dataset. The aim was to assess the individual additive predictive value of cognition, cortical structure information, and brain age gap to a clinical Cox proportional hazards model developed by Nelson *et al.* (35). The clinical model consisted of poor functioning (Global Assessment of Functioning [GAF]), duration of symptoms prior to service entry, and UHR subgroup. The aim of this study was to quantify the benefits of including additional modalities in predicting transition to FEP in the PACE 400 cohort rather than finding the most generalizable prediction model.

METHODS AND MATERIALS

The PACE 400 Study

The PACE 400 study is the first long-term follow-up of a UHR cohort (up to 15 years after entry to the PACE clinic). The PACE 400 cohort (35) (N = 416) comprised all patients at UHR for psychosis participating across 7 studies [3 intervention (36–38), 4 cohort (39–42)] at the PACE clinic in Melbourne, Australia, between 1993 and 2006.

The enrollment criteria and assessment of UHR status at baseline are outlined in the Supplement. The main outcome of interest in the PACE 400 study was transition to psychotic disorder. Details on how psychosis status was determined in the PACE 400 study are described in the Supplement. Time to follow-up ranged from 2.4 to 18.6 years after baseline, with a mean follow-up time of 7.5 years (SD = 3.2 years) (35). The study combined individual information from multiple substudies across multiple domains including clinical assessments, cognition, neuroimaging, and in some cases fluid biospecimens. Previous studies have investigated cortical structure in the PACE 400 cohort but either in a smaller cohort (43) or only in individuals who did not transition to psychosis (44). Furthermore, cognitive predictors in the PACE 400 cohort were previously assessed in a univariate analysis (45) but not in terms of their additive predictive value to a clinical prediction model.

Measures

Clinical Measures. At baseline, negative symptoms were assessed using the Scale of Assessment for Negative Symptoms (46), positive symptoms were assessed with the Brief Psychiatric Rating Scale, psychotic subscale (47) and the Comprehensive Assessment of At Risk Mental States (CAARMS) (1), and depressive symptoms were assessed using the Hamilton Rating Scale for Depression (48).

Functioning. Functioning was determined using the Quality of Life Scale (49) and the GAF (50).

Structural Imaging. Details on MRI scanners used for MRI acquisition, cortical reconstruction, and volumetric segmentation using FreeSurfer (51) are outlined in the Supplement.

The neuroimaging measures demonstrated a large variance between scanner sites due to different types of scanners that were used (Figure S1). We applied the ComBat method (52) prior to our analysis to harmonize neuroimaging measures across sites. The ComBat method assumes an additive and multiplicative scanner or site effect which can be estimated from the data using conditional posterior means and subsequently removed (53). ComBat requires a sufficient sample size from each site or scanner to successfully estimate the multiplicative effect. The outcome measure of transitioning to FEP was included as a covariate to align the distributions of individuals transitioning to FEP and individuals who did not transition across sites (53). To reduce the dimension of the feature space for each neuroimaging domain, we applied bilateral principal component analysis (PCA) (54). We also included cortical thickness values for fusiform, superior temporal, and paracentral regions as candidate predictors because they have been associated with psychosis conversion in the ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis) clinical high risk for psychosis initiative (55).

Cognition. IQ at baseline was measured using a range of age-appropriate scales across studies (56) including the Wechsler Adult Intelligence Scale-Revised (57), the Wechsler Abbreviated Scale of Intelligence (58), or the Wechsler Intelligence Scale for Children (59). Verbal list learning and memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT) (60). Here, we used the age-adjusted scores for Wechsler Adult Intelligence Scale-Revised subtests Arithmetic and Digit Symbol Coding as well as the total score from a

3-trial version of the RAVLT as cognitive predictors. Verbal learning and memory (RAVLT), processing speed (Digit Symbol Coding), and auditory verbal working memory (Arithmetic) have shown strong associations with transition to psychosis and changes in functioning in previous studies (24,61,62).

Brain Age Gap. We used the publicly available pretrained ENIGMA brain age model (https://photon-ai.com/enigma_brainage) to estimate the brain age in the PACE 400 cohort. The model was trained using ridge regression to estimate normative models of the association between chronological age and 14 subcortical gray matter regions (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus), 2 lateral ventricles, 68 cortical thickness measures, 68 surface area measures, and total intracranial volume in a healthy sample of 952 males (16 scanning sites) and 1236 females (22 scanning sites) aged 18 to 75 years (63). Standardized protocols were used for image processing and feature extraction across sites (http://enigma.ini.usc.edu/protocols/imaging-protocols/). To control for regression dilution, a common phenomenon in brain age prediction models that results in a systematic overestimation of the brain age for younger individuals and a systematic underestimation of the brain age for older individuals (64), we included chronological age as a covariate in our analysis as suggested by the ENIGMA brain age model (63). An overview of the estimated brain age gap for individuals with neuroimaging in the PACE 400 cohort using the ENIGMA Photon Brain Age Model without correction and with correction by removing the linear trend caused by chronological age is shown in Figure S2.

Model

Survival analysis was applied to analyze transition to FEP. Cox proportional hazards regression (65) was used to investigate the predictive value of clinical predictors combined with cognition, neuroimaging, or brain age gap. We fitted a base model that included 3 clinical variables as well as enhanced models that added 1 of the following modalities: CAARMS subscales, cognition, MRI, or brain age gap. For each additional modality, we initially added 1 additional predictor and in a further analysis a maximum of 2 predictors to remain within a maximum of 5 predictors (3 clinical predictors plus 2 predictors for each additional modality), which resulted in 10 to 15 events per predictor (66–70). The analysis plan is summarized in Figure 1.

The 3 predictors of GAF, duration of symptoms prior to service entry, and UHR subgroup were included in the base model based on the univariate analysis in Nelson *et al.* (35). More information on the clinical predictors is provided in the Supplement. Regarding the additional modalities, the CAARMS subscales Disorders of Thought Content and Conceptual Disorganization, which were the most significant additional variables identified in Nelson *et al.* (35), were included to provide additional information on the severity of positive psychotic symptoms and to control for the effect of adding more variables to the base model. The first bilateral principal component of each MRI domain as well as cortical thickness values for left fusiform, right superior temporal, and left and right paracentral regions were included as neuroimaging predictors. Brain age gap plus chronological age was included as neuroanatomical predictor. For the subset

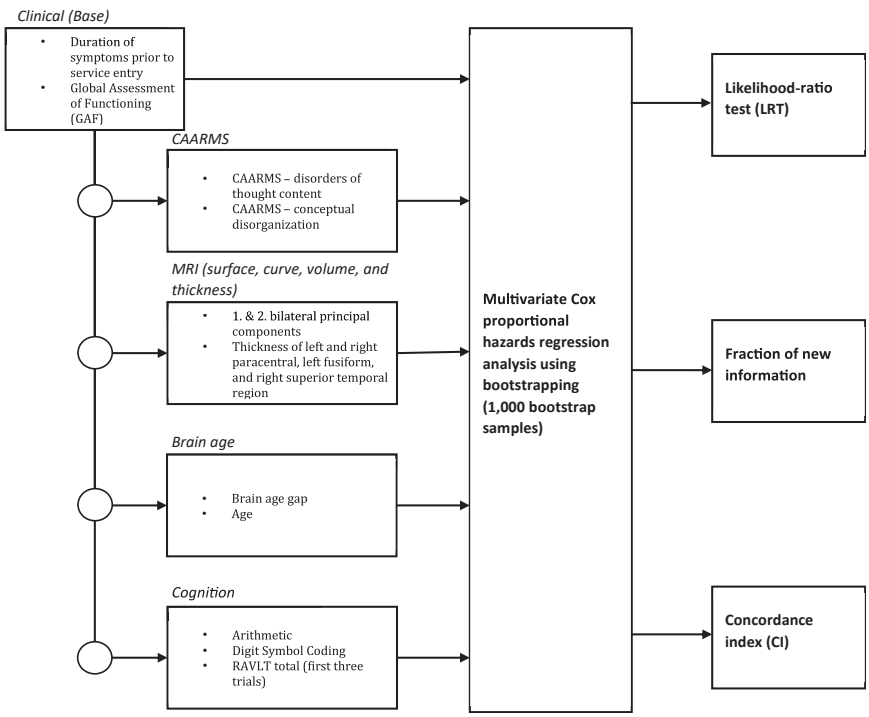

Figure 1. Study plan using nested Cox proportional hazards regression models, internal validation, and nested models evaluation. Study plan using nested Cox proportional hazards regression models with a base model including the global assessment of functioning (GAF), duration of symptoms prior to service entry, and ultra-high risk group status as clinical variables as well as full models that contained the 3 clinical variables and 1 of the additional modalities: neuroimaging (magnetic resonance imaging [MRI]), brain age gap, or cognition. We also fitted a model containing the 3 clinical variables plus the Comprehensive Assessment of At Risk Mental States (CAARMS) subscales Disorders of Thought Content and Conceptual Disorganization to control for the effect of adding 2 variables to the base model. The full models were subsequently compared to the base model using the likelihood-ratio test, the fraction of new information, and the concordance index. RAVLT, Rey Auditory Verbal Learning Test.

of participants with cognition measures, the base model was repeated and compared in a separate sample with 2 enhanced models: first a model adding CAARMS subscales and second a model adding cognition predictors measured by age-adjusted scores for Wechsler subtests Arithmetic and Digit Symbol Coding and the RAVLT total score. Due to a difference in the number of participants with neuroimaging and cognition data, we performed our analysis in separate neuroimaging and cognition datasets from the PACE 400 sample. Each model was internally validated using bootstrapping (1000 samples) (71).

The enhanced models were then compared to the base model (GAF, duration of symptoms prior to service entry, and UHR subgroup) to assess the additional predictive value of each modality. For each enhanced model, the likelihood-ratio test (LRT) for added value was obtained by comparing log likelihoods of the base and full models. The significance level for p values from the LRT was $<.05$. We also determined the fraction of new information as the proportion of total predictive information that was added by cognition, MRI predictors, or brain age gap. More information on the calculation of the fraction of new information is provided in the Supplement. Before the analysis, we checked whether all variables included in the analysis and the variable describing the treatment groups (treatment-as-usual participants and participants who received trial treatments) satisfied the proportional hazards assumption. The analysis was performed in R (72) using the rms (72) and glmnet (73) package. Code for this analysis is available at https://github.com/preempt-centre-for-research-excellence/MultiPredModelPACE400.

RESULTS

Table 1 details the descriptive statistics of the neuroimaging and cognition samples at baseline and follow-up. A total of 212 individuals at UHR for psychosis (49% female) were included in the neuroimaging dataset (age at baseline [mean ± SD] 19 ± 5 years). There were 65 transitioned cases (31%) in the neuroimaging sample, with an average time to transition of 168 days (SD = 461 days). The cognition dataset contained a total of 94 individuals at UHR for psychosis (51% female) with an average age of 21 years (SD = 3.5 years). In the cognition sample, there were 39 transitioned cases (41%) with an average time to transition of 217 days (SD = 528 days). The demographic and clinical characteristics of the total sample (N = 416) have been reported and discussed in detail in a previous publication (35).

Clinical Measures Plus Neuroimaging

Table 2 lists the regression coefficients and test scores after internal validation using bootstrapping for clinical and neuroimaging variables in a multivariate Cox regression model to predict transition to FEP in PACE 400. The base model with GAF, duration of symptoms prior to service entry, and UHR subgroup as predictors in the neuroimaging sample achieved a concordance index of 0.68. There was strong evidence that all 3 individual predictors had an effect on the risk for transition to FEP (GAF: hazard ratio [HR] = 0.51 [95% CI: 0.33, 0.71], p = .001; duration of symptoms prior to service entry, log-transformed: HR = 1.68 [95% CI: 1.16, 2.64], p = .015; UHR subgroup, brief limited intermittent psychotic symptoms vs. vulnerability: HR = 3.13 [95% CI: 1.26, 10.50], p = .017; UHR subgroup, attenuated psychosis vs. vulnerability: HR = 1.28 [95% CI: 0.62, 3.55], p = .017).

Table 1. Descriptive Information About the Neuroimaging and Cognition Samples at Baseline and Follow-Up

	Cognition, n = 94	MRI, n = 212
Nonstandard (Trial) Intervention Treatment	24% (23)	37% (78)
Sex, Female	51% (48)	49% (104)
Age at Baseline, Years	21.1 ± 3.5	19.9 ± 3.5
Days Between Symptom Onset and First Contact With PACE	564.2 ± 1056.4	430.9 ± 632.5
UHR Subgroup		
Any BLIPS	24% (23)	16% (34)
APS or APS+vulnerability	59% (55)	68% (144)
Vulnerability	17% (16)	16% (34)
Clinical Measures		
BPRS total	43.4 ± 7.5	46.2 ± 9.0
SANS total	18.3 ± 13.6	19.3 ± 11.9
GAF	62.3 ± 14.5	59.2 ± 11.7
QLS total	73.3 ± 22.3	75.1 ± 20.3
CAARMS Disorders of Thought Content, severity	2.1 ± 1.1	2.0 ± 1.1
CAARMS Perceptual Abnormalities, severity	1.9 ± 1.5	2.1 ± 1.5
CAARMS Conceptual Disorganization, severity	2.1 ± 1.1	1.9 ± 1.0
Cognition		
Coding	9.3 ± 2.5	–
Arithmetic	8.7 ± 3.1	–
RAVLT total	28.6 ± 6.3	–
Brain Age Gap		−0.3 ± 7.4
Follow-Up		
Transition to psychosis	41% (39)	31% (65)
Follow-up time, days	4055.3 ± 320.6	3052.8 ± 1066.0
Time to transition, days	217.4 ± 528.0	167.8 ± 460.9
SOFAS score	62.9 ± 17.0	69.0 ± 16.0

Values are presented as % (n) or mean ± SD.
APS, attenuated psychotic symptoms; BLIPS, brief limited intermittent psychotic symptoms; BPRS, Brief Psychiatric Rating Scale; CAARMS, Comprehensive Assessment of At Risk Mental States; GAF, Global Assessment of Functioning; MRI, magnetic resonance imaging; PACE, Personal Assessment and Crisis Evaluation; QLS, Quality of Life Scale; RAVLT, Rey Auditory Verbal Learning Test; SANS, Scale of Assessment for Negative Symptoms; SOFAS, Social and Occupational Functioning Assessment Scale; UHR, ultra-high risk.

The addition of the CAARMS subscales Disorders of Thought Content or Conceptual Disorganization to the base model increased the model fit by 3% to 4%, adding a marginal amount of new information (LRT disorders of thought content: p = .240, LRT conceptual disorganization; p = .302). The addition of the first bilateral principal component of cortical surface area, curvature, volume, or thickness did not add new information to the clinical model (LRT surface area: p = .946, LRT curve: p = .789, LRT volume: p = .687, LRT thickness: p = .463). Subsequently, a combination of the first principal component of thickness and volume or the first and second

Table 2. Results After Internal Validation (Bootstrapping n = 1000) for Clinical and Neuroimaging Predictor Variables in the Multivariate Cox Proportional Hazards Regression Analysis of Transition to Psychosis, n = 212

	Base		Base + Disorders of Thought Content		Base + Conceptual Disorganization		Base + MRI Surface PC		Base + MRI Curve PC		Base + MRI Volume PC		Base + MRI Thickness PC		Base + Thickness Paracentral Left		Base + Thickness Paracentral Right		Base + Thickness Superior Temporal Right		Base + Thickness Fusiform Left	
Predictor Variable	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*
Duration of Symptoms Prior to Service Entry–Log-Transformed	1.68	.015[a]	1.68	.021[a]	1.64	.025[a]	1.68	.019[a]	1.67	.021[a]	1.66	.018[a]	1.65	.019[a]	1.66	.018[a]	1.67	.017[a]	1.65	.024[a]	1.70	.019[a]
GAF	0.51	.001[a]	0.53	.002[a]	0.52	.001[a]	0.51	.001[a]	0.51	.001[a]	0.50	.001[a]	0.50	.001[a]	0.50	.002[a]	0.50	.001[a]	0.50	<.001[a]	0.51	<.001[a]
UHR Subgroup		.017[a]		.050		.024[a]		.015[a]		.014[a]		.014[a]		.017[a]		.031[a]		.027[a]		.017[a]		.024[a]
BLIPS vs. vulnerability	3.13		2.56		3.08		3.12		3.12		3.10		3.04		3.10		2.87		3.05		2.99	
Attenuated psychosis vs. vulnerability	1.28		1.11		1.35		1.28		1.28		1.26		1.26		1.25		1.21		1.29		1.26	
CAARMS Disorders of Thought Content			1.37	.292																		
CAARMS Conceptual Disorganization					1.14	.389																
Bilateral PC MRI Variable							0.99	.954	1.05	.819	0.93	.728	1.12	.491	0.78	.164	0.77	.140	0.87	.468	0.76	.131
Regression Analysis Results																						
LR χ^2	35.00		36.38		36.07		35.00		35.07		35.16		35.54		37.44		37.28		35.67		37.21	
Fraction of New Information	–		0.04		0.03		0.00		0.00		0.01		0.02		0.07		0.06		0.02		0.06	
Concordance Index	0.68		0.68		0.68		0.68		0.68		0.68		0.68		0.69		0.69		0.68		0.68	

For each full model, the likelihood-ratio (LR) test was obtained by comparing log likelihoods of the base and full models. The fraction of new information is the proportion of total predictive information in clinical plus MRI that was added by MRI. It was calculated as follows: 1 − base LR χ^2/full LR χ^2.

BLIPS, brief limited intermittent psychotic symptoms; CAARMS, Comprehensive Assessment of At Risk Mental States; GAF, Global Assessment of Functioning; HR, hazard ratio; MRI, magnetic resonance imaging; PC, principal component; UHR, ultra-high risk.

[a]Significance level for LR test: $p < .05$.

principal components for cortical thickness because cortical thickness and volume appeared to add the most information to the clinical model of the 4 cortical domains, resulted in a marginal increase in new information (2%) with no effect (LRT thickness and volume: $p = .752$, LRT first and second principal component cortical thickness: $p = .701$) (see Table S1).

Of the 4 individual regions identified in the ENIGMA clinical high risk for psychosis initiative as being associated with psychosis conversion, cortical thickness for the right paracentral region added the most new information to the clinical model (7%) with an increase in the concordance index to 0.69. However, adding the regional cortical thickness values individually as predictors to the base model did not have a significant effect on the model fit (LRT right paracentral: $p = .119$, LRT left paracentral: $p = .131$, LRT right superior temporal: $p = .412$, LRT left fusiform: $p = .137$). The largest addition of new information to the base model, 12%, was achieved by adding cortical thickness values of the left paracentral and left fusiform together, although with small effect (LRT: $p = .101$) (see Table S1).

Clinical Measures Plus Brain Age Gap

Table 3 lists the regression coefficients and test scores after internal validation using bootstrapping for clinical and brain age gap variables. Adding brain age gap and chronological age to the clinical model resulted in 7% of new information and an increase in the concordance index to 0.69, although this was not significant (LRT: $p = .291$). The fraction of new information was predominantly due to the addition of age as shown by the individual analysis in Table 3.

Clinical Measures Plus Cognition

Table 4 lists the regression coefficients and test scores after internal validation using bootstrapping for clinical and cognition variables. The base model with GAF, duration of symptoms prior to service entry, and UHR subgroup as predictors in the cognition sample achieved a concordance index of 0.69. In contrast to the base model in the neuroimaging dataset, there was strong evidence that in the base model only GAF had an effect on the risk of transition to FEP (GAF: HR = 0.33 95% CI [0.15, 0.54], $p = .001$) but not duration of symptoms prior to service entry or UHR subgroup categories. Similar to the results in the neuroimaging dataset, the addition of the CAARMS subscales Disorders of Thought Content or Conceptual Disorganization to the base model only marginally increased the model fit by 1%–4% (LRT disorders of thought content: $p = .305$, LRT conceptual disorganization: $p = .605$) with no improvement in the concordance index. Adding the RAVLT total score and the age-adjusted scores for Arithmetic and Digit Symbol Coding individually (+0%–9%, LRT Digit Symbol Coding: $p = .492$, LRT Arithmetic: $p = .113$, LRT RAVLT total: $p = .975$) or combined (+2–16%, see Table S2) as cognitive predictors to the base model did not result in any large improvement of the model fit.

DISCUSSION

In this study, we assessed the predictive value of additional modalities including cognition, structural neuroimaging, or the neuroanatomical measure brain age gap to a base clinical model of transition to FEP (GAF, duration of symptoms prior to service entry, and UHR subgroup) in the PACE 400 sample, derived using Cox proportional hazards regression models. The cognitive variables, verbal learning and memory (RAVLT), processing speed (Digit Symbol Coding), and auditory verbal working memory (Arithmetic), added a marginal amount of additional predictive information to the clinical model. The addition of neuroimaging measures such as cortical surface area, curvature, volume, or thickness resulted in no significant improvement of the model fit or accuracy. The neuroimaging composite measure brain age gap plus chronological age increased the amount of variance that was explained by the model by 7% and increased the concordance index from 0.68 to 0.69, but this effect was predominantly a result of the addition of chronological age as a predictor rather than specific differences in brain structure.

Previous studies have shown that compared to unimodal approaches, multimodal approaches, particularly machine learning models, may help more accurately estimate the individual transition risk in UHR samples (11,15,74,75). Most commonly, the complementary predictive value of cognition, neuroimaging, and genetic features has been investigated. Our results suggest that the combination of MRI and clinical assessment only marginally improved the fit of a psychosis transition prediction model in the PACE 400 cohort. The combination of neuroimaging with the base clinical model resulted in a similar model fit and concordance index when controlling for adding the next-most-significant clinical variables identified in Nelson *et al.* (35), the CAARMS subscales Disorders of Thought Content and Conceptual Disorganization.

The discrepancy in outcomes with previous multimodal UHR studies could be related to the heterogeneity of the PACE 400 cohort in that it is a collection of cohort studies and clinical trials that were conducted over an extended period of time (14 years). Moreover, studies that have investigated the benefit of multimodal prediction models have either suggested only a marginal improvement compared to unimodal approaches (74) or used a small sample size (75), thus resulting in a strong risk of misestimation (76,77). More promising results have been achieved when different modalities have been stacked (15), e.g., using generalized stacked models (11) because stacking determines how to optimally combine the predictions from each modality. However, stacked Cox proportional hazards regression models are particularly complex due to the inclusion of time-to-event information. Furthermore, previous studies have suggested that the change in cortical structure, especially cortical thickness, may be a more suitable predictor for transition to psychosis than cortical measures assessed at baseline (27,78,79).

The addition of cognitive measures to the clinical model did not result in an improvement of model fit. Our results are consistent with previous studies that have analyzed the predictive value of cognition in the PACE 400 cohort (45,61), which have shown that cognition is not a strong predictor of transition to psychosis. Our results on the additive predictive value of cognition are restricted by the differences in cognitive batteries used across studies and the resultant small size of the cognition sample in this study. The neuroanatomical measure brain age gap did not improve model accuracy when

Table 3. Results After Internal Validation (Bootstrapping *n* = 1000) for Clinical and Brain Age Gap Predictor Variables in the Multivariate Cox Proportional Hazards Regression Analysis of Transition to Psychosis, *n* = 212

	Base		Base + Disorders of Thought Content		Base + Conceptual Disorganization		Base + Brain Age Gap		Base + Age		Base + Brain Age Gap + Age	
Predictor Variable	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*
Duration of Symptoms Prior to Service Entry–Log Transformed	1.68	.015[a]	1.68	.021[a]	1.64	.025[a]	1.67	.020[a]	1.71	.022[a]	1.70	.024[a]
GAF	0.51	.001[a]	0.53	.002[a]	0.52	.001[a]	0.51	.001[a]	0.49	<.001[a]	0.49	.001[a]
UHR Subgroup		.017[a]		.050		.024[a]		.017[a]		.003[a]		.004[a]
BLIPS vs. vulnerability	3.13		2.56		3.08		3.14		3.19		3.21	
Attenuated psychosis vs. vulnerability	1.28		1.11		1.35		1.28		1.13		1.13	
CAARMS Disorders of Thought Content			1.37	.292								
CAARMS Conceptual Disorganization					1.14	.389						
Brain Age Gap							1.03	.879			1.04	.847
Age									0.74	.151	0.74	.180
Regression Analysis Results												
LR χ^2	35.00		36.38		36.07		35.03		37.42		37.47	
Fraction of New Information	–		0.04		0.03		0.00		0.07		0.07	
Concordance Index	0.68		0.68		0.68		0.68		0.69		0.69	

For each full model, the likelihood-ratio (LR) test was obtained by comparing log likelihoods of the base and full models. The fraction of new information is the proportion of total predictive information in clinical plus brain age gap that was added by brain age gap. It was calculated as follows: 1 − base LR χ^2/full LR χ^2.

BLIPS, brief limited intermittent psychotic symptoms; CAARMS, Comprehensive Assessment of At Risk Mental States; GAF, Global Assessment of Functioning; HR, hazard ratio; PC, principal component; UHR, ultra-high risk.

[a]Significance level for LR test: $p < .05$.

Table 4. Results After Internal Validation (Bootstrapping *n* = 1000) for Clinical and Cognition Predictor Variables in the Multivariate Cox Proportional Hazards Regression Analysis of Transition to Psychosis, *n* = 127

	Base		Base + Disorders of Thought Content		Base + Conceptual Disorganization		Base + Digit Symbol Coding		Base + Arithmetic		Base + RAVLT Total	
Predictor Variable	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*
Duration of Symptoms Prior to Service Entry–Log Transformed	1.47	.145	1.49	.153	1.47	.150	1.44	.180	1.52	.134	1.47	.166
GAF	0.33	.001[a]	0.35	.002[a]	0.33	.001[a]	0.31	.001[a]	0.35	.002[a]	0.33	.001[a]
UHR Subgroup		.712		.839		.684		.677		.845		.760
BLIPS vs. vulnerability	1.63		1.34		1.71		1.72		1.42		1.63	
Attenuated psychosis vs. vulnerability	1.24		1.04		1.33		1.26		1.21		1.24	
CAARMS Disorders of Thought Content			1.21	.338								
CAARMS Conceptual Disorganization					1.09	.716						
Cognition Variable							1.15	.550	0.61	.178	1.01	.977
Regression Analysis Results												
LR χ^2	26.94		27.99		27.21		27.41		29.46		26.94	
Fraction of New Information	–		0.04		0.01		0.02		0.09		0.00	
Concordance Index	0.69		0.69		0.61		0.68		0.69		0.69	

For each full model, the likelihood ratio (LR) test was obtained by comparing log-likelihoods of the base and full models. The fraction of new information is the proportion of total predictive information in clinical plus cognition that was added by cognition. It was calculated as follows: 1 − base LR χ^2/full LR χ^2.

BLIPS, brief limited intermittent psychotic symptoms; CAARMS, Comprehensive Assessment of At Risk Mental States; GAF, Global Assessment of Functioning; HR, hazard ratio; PC, principal component; RAVLT, Rey Auditory Verbal Learning Test; UHR, ultra-high risk.

[a]Significance level for LR test: $p < .05$.

considered together with age. Our findings are consistent with the results from the North American Prodromal Longitudinal Study, which found that the predictive variance of brain age gap overlapped entirely with that of age (4). Furthermore, our results in terms of brain age gap are limited by the usage of a publicly available external model that was trained on healthy individuals aged 18 to 75 years. Although the ENIGMA Photon Brain Age model proved to be accurate in a previous study, the lack of a validation sample in our cohort and the slightly different age range, with an average age of 20 years (SD = ±3.5 years), may have influenced our results. Finally, the predictive value of brain age gap for transition to psychosis could be reduced by the large age range in our sample resulting in a discrepancy between predictive information in similar brain age gap values for younger and older participants. This could be accounted for by dividing the sample into age groups in addition to adding age as a covariate, but this was not done in this sample due to the small sample size.

Our study is limited by the low number of events (transitioned cases) in the subset of the PACE 400 cohort that had cognitive or neuroimaging data available, highlighting a key drawback to adding modalities to the structured clinical assessment routine because they multiply the costs and workload of the assessment. The low number of events could partially explain the lack of predictive benefit of multimodal models that was observed in this study because the characteristics of individuals with complete data may differ from individuals who were excluded from this study. A low number of events restricts the number of potential predictors, the optimization of the model fit, and the validation of the fitted model. Additionally, we did not account for nonstandard treatment due to randomization to intervention trials that are part of the PACE 400 sample because testing the proportional hazards assumption did not indicate a need for stratification based on treatment received. Moreover, a sensitivity analysis in the original PACE 400 study indicated the same results for the treatment-as-usual participants (i.e., excluding 244 who had received trial treatments) and the entire cohort (35). Another limitation is the possibility that some transitioned cases were not detected, i.e., if they were unavailable for interview and had not attended a public mental health service (35).

Another major limitation of our study was the heterogeneity in neuroimaging measures due to different MRI scanners being used at assessment sites. Figure S1 illustrates the inherited bias across sites for cortical thickness in the right rostral middle frontal region. Harmonizing the neuroimaging measures across scanner sites using the ComBat method successfully removed the site bias, although the ComBat method has been shown to have the potential to cause distortion in the absence of a scanner or site effect (80) and is outperformed by traveling-subject-based harmonization methods (81). The need for harmonization raises a number of questions with regard to the clinical application of multimodal models for the prediction of transition to psychosis in individuals at UHR for psychosis. Harmonization performs well during the implementation and evaluation phase of a model because the distributions of each scanner or site can be determined in the training and test set. However, harmonization in a clinical application relies on a priori knowledge of the deployed scanner to remove the inherited bias. Moreover, there is no agreed-upon way to standardize MRI measures within a cross-validation framework used to train machine learning models (33). Thus, the heterogeneity in MRI measures across sites and scanners severely limits the broad clinical applicability of multimodal prediction models that include neuroimaging and highlights the need for local recalibrations of models.

Conclusions

In sum, our results show that the inclusion of neuroimaging or cognitive information in a risk model that estimates the proportional hazard of transition to psychosis in individuals at UHR for psychosis in the PACE 400 study appears to add little information to improve the fit of the clinical-based model. These findings raise the question of whether adding baseline cognitive and structural MRI assessments provides sufficient additional predictive information to warrant the associated computational and economical costs and the increased workflow complexity of actioning these assessments in a clinical setting apart from their predictive value in a clinical setting. However, it is important to acknowledge that our findings are limited by the constraints on methodological choices given the nature of the cohort that could have decreased the importance of our findings.

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