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Publication Date

2021

DOI

10.1016/j.schres.2020.09.022

Peer reviewed

HHS Public Access

Author manuscript

Schizophr Res. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Schizophr Res. 2021 January ; 227: 95–100. doi:10.1016/j.schres.2020.09.022.

Incorporating cortisol into the NAPLS2 individualized risk calculator for prediction of psychosis

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Abstract

Background: Risk calculators are useful tools that can help clinicians and researchers better understand an individual's risk of conversion to psychosis. The North American Prodrome Longitudinal Study (NAPLS2) Individualized Risk Calculator has good predictive accuracy but could be potentially improved by the inclusion of a biomarker. Baseline cortisol, a measure of hypothalamic-pituitary-adrenal (HPA) axis functioning that is impacted by biological vulnerability to stress and exposure to environmental stressors, has been shown to be higher among individuals at clinical high-risk for psychosis (CHR-P) who eventually convert to psychosis than those who do

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Author contribution statement

T.D.C. and E.F.W. conceived of and proposed the present analysis. M.W. performed the statistical analyses and wrote the manuscript with the help of all authors. All authors contributed to and have approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

not. We sought to determine whether the addition of baseline cortisol to the NAPLS2 risk calculator improved the performance of the risk calculator.

Methods: Participants were drawn from the NAPLS2 study. A subset of NAPLS2 participants provided salivary cortisol samples. A multivariate Cox proportional hazards regression evaluated the likelihood of an individual's eventual conversion to psychosis based on demographic and clinical variables in addition to baseline cortisol levels.

Results: A total of 417 NAPLS2 participants provided salivary cortisol and were included in the analysis. Higher levels of cortisol were predictive of conversion to psychosis in a univariate model (C-index = 0.59, HR = 21.5, *p*-value = 0.004). The inclusion of cortisol in the risk calculator model resulted in a statistically significant improvement in performance from the original risk calculator model (C-index = 0.78, SE = 0.028).

Conclusions: Salivary cortisol is an inexpensive and non-invasive biomarker that could improve individual predictions about conversion to psychosis and treatment decisions for CHR-P individuals.

Keywords

Cortisol; clinical high-risk; psychosis; prediction; survival analysis; risk calculator

Introduction

The ability to predict conversion to psychosis from the clinical high-risk state (CHR-P) remains an important goal for clinicians and researchers. Having a better understanding of who might convert can help inform how to allocate resources and inform treatment decisions in high-risk populations. In recent years, several "risk calculator" models have been proposed to quantify an individual's probability of converting to psychosis based on clinical, demographic, and neurocognitive measures (Cannon et al., 2016; Ciarleglio et al., 2019; Fusar-Poli et al., 2017; Zhang et al., 2018). We previously published one such calculator with data from the second phase of the North American Prodromal Longitudinal Study (NAPLS2) (Cannon et al., 2016). This risk calculator achieved a concordance index (C-index, a measure of accuracy analogous to area under the curve) of 0.71 and was validated in an external sample with a C-index of 0.79 (Carrión et al., 2016). This performance is comparable to the accuracy of subsequently published psychosis prediction models that had C-indices of 0.73 (Ciarleglio et al., 2019; Fusar-Poli et al., 2017) and 0.744 (Zhang et al., 2018).

A major advantage of these risk calculator models is that they are instantiated by clinician-administered assessments that are relatively inexpensive and efficient to administer. These models perform well and are comparable to recent risk calculator models developed for use in other medical disciplines such as oncology and cardiology (Nickson et al., 2018; Wright et al., 2019). There is, however, room for improvement to use more objective measures to better estimate an individual's risk for conversion to psychosis from the clinical high-risk period. As discussed in Cannon et al. (Cannon et al., 2016), the addition of biological markers may be useful in this regard. In addition, the inclusion of a biomarker could expand the utility of the risk calculator into the realm of drug development for the CHR-P state,

given the Food and Drug Administration's (FDA) preference of biomarker identification for drug development (Brady et al., 2019).

It is well-established that stress plays a large role in the development and progression of many forms of psychopathology, especially in psychotic disorders, and the biological mechanisms therein have been the focus of a large body of research (Aiello et al., 2012). A biological vulnerability to stress in combination with environmental stressors and distress related to experiencing prodromal symptoms may exacerbate and progress symptoms and functional decline (Walker and Diforio, 1997). The neural diathesis-stress model describes the role of the hypothalamic-pituitary-adrenal (HPA) axis in both predisposing an individual to stress sensitivity and responding to environmental stressors in psychotic disorders (Walker et al., 2008). This model was recently refined to account for the neurodevelopmental changes that occur over time and affect HPA axis functioning as psychotic illnesses progress (Pruessner et al., 2017; Walker et al., 2008). Cortisol levels are frequently used as a measure of HPA axis activity (Spencer and Deak, 2017). Measuring cortisol is relatively inexpensive and non-invasive, and can be measured through saliva, blood, or urine samples (Pruessner et al., 2017), making it feasible for implementation in clinical use.

Several studies have demonstrated cortisol abnormalities for individuals with psychotic disorders (Pruessner et al., 2017; Walker et al., 2008; Walker and Diforio, 1997); however, less is known about the role of the HPA axis and basal cortisol in the CHR-P population. Studies have shown elevated levels of basal cortisol in CHR-P individuals as compared to healthy controls (Carol and Mittal, 2015), higher levels of basal cortisol for unmedicated CHR-P individuals as compared to medicated CHR-P individuals (Sugranyes et al., 2012), an association between cortisol levels and symptom severity, and higher levels of basal cortisol in individuals who converted to psychosis from the CHR-P period as compared to nonconverters (Walker et al., 2013). Basal cortisol levels have been shown to be higher in converters as compared to nonconverters even after controlling for exposure to stressors, which may indicate metabolic abnormalities or an amplification of normal maturational processes in CHR converters, both of which are associated with increased cortisol levels (Cullen et al., 2020).

In the present study, we sought to determine how the addition of cortisol to the NAPLS2 risk calculator would affect prediction accuracy of conversion to psychosis in a CHR-P sample. As we previously found that basal cortisol levels were higher in CHR-P converters as compared to nonconverters in the NAPLS2 sample (Walker et al., 2013), we hypothesized that the inclusion of cortisol would increase the predictive accuracy of the existing model, with higher levels of baseline cortisol, in combination with other risk factors, being associated with a higher probability of conversion within a two-year period.

Materials and Methods

Participants

Participants were drawn from the second phase of the North American Prodrome Longitudinal Study (NAPLS2) (Addington et al., 2012). NAPLS2 is an 8-site observational consortium study examining the predictors and mechanisms related to conversion to

psychosis in the clinical high-risk population. Participants were individuals aged 12–35 who met criteria for a prodromal risk syndrome as determined by the Criteria of Prodromal States (COPS) (McGlashan et al., 2010) and as measured by the Structured Interview for Psychosis-risk Syndromes (SIPS) (McGlashan et al., 2001; Miller et al., 2002). Clinical assessments including the SIPS and the Scale of Psychosis-risk Symptoms (SOPS) (Hawkins et al., 2004), which is contained within the SIPS, were administered at 6-month intervals, or at the time of conversion to psychosis, during the 24-month study. Participants were excluded if they met criteria for any previous DSM-IV (Castillo et al., 2007) diagnosis of a psychotic disorder, any pervasive developmental disorder, current drug or alcohol dependence, or the presence of a neurological disorder. The detailed methods of the overall NAPLS2 study have been described previously (Addington et al., 2012).

Risk Calculator Assessments

The original risk calculator was developed with eight variables that were previously shown to be associated with conversion to psychosis. These variables were: age; positive symptom severity on SIPS items P1 and P2 (e.g. unusual thought content and suspiciousness); score on the Brief Assessment of Cognition in Schizophrenia (BACS) symbol coding test (Keefe et al., 2008); score on the Hopkins Verbal Learning Test-Revised (HVLT-R) (Benedict et al., 1998); decline in social functioning during the prior year as measured by the Global Functioning Social scale (GFS) (Cornblatt et al., 2007); stressful life events as measured by the Research Interview Life Events Scale (Dohrenwend et al., 1978); childhood traumas as measured by the Childhood Trauma and Abuse Scale (Janssen et al., 2004); and family history of psychotic disorder in a first-degree relative (Cannon et al., 2016). The model was derived from the NAPLS2 sample and was also validated in an external sample (Carrión et al., 2016). Detailed methods of the risk calculator have been described previously (Cannon et al., 2016).

Cortisol

For details on the saliva collection and salivary cortisol assay, see the previous report on NAPLS2 (Walker et al., 2013). In brief, participants were provided with dietary instructions for the evening before and morning of sampling encouraging them to avoid food and beverages that can alter cortisol levels (caffeine, alcohol, dairy products, and nonprescription medications). Compliance with these instructions was confirmed by verbal query prior to saliva collection via passive drool. In the present study, none of the available assayed samples were excluded based on failure to adhere to protocol instructions. Saliva samples were obtained three times at baseline in the clinic, approximately on the hour (i.e., over two hours) with an average onset time of 10:00AM (SD = 26 minutes). (Walker et al., 2013). Multiple saliva samples (n = 3) were obtained to derive an average and increase the reliability of the cortisol estimate (Tornhage, 2002). The three salivary cortisol samples were all correlated with one another, indicating reliability of the assay (Walker et al., 2013).

Saliva was stored at −20°C and at time of assay rapidly thawed and assayed for salivary cortisol (μg/dl) using a highly sensitive enzyme immunoassay (Salimetrics, State College, PA). All samples were assayed in duplicate. Mean cortisol across the samples was derived for each subject. Due to the normal diurnal decline in cortisol, there is a significant inverse

relation of cortisol with time at collection. Because of differences among subjects in time of collection onset, residual mean cortisol values were computed via regression to control for time.

Statistical Analysis

A multivariate Cox proportional hazards regression was used to determine the likelihood of an individual's conversion to psychosis within a 2-year period. The original risk calculator was comprised of eight variables to ensure there were a least 10 converters per predictor variable. To continue this method of preserving degrees of freedom for the present analysis, the original model was pruned to exclude total traumas, stressful life events, and family history, as these terms were not significant in the original model at either the multivariate or the univariate level while all other predictors were significant at both the multivariate and the univariate level. To ensure that the cortisol term did not subsume the variance introduced by the pruned terms, the full unpruned model (i.e., including all of the original variables plus cortisol) was compared alongside the pruned model. The primary model in the present analysis included the following variables after pruning: age, SIPS items P1 and P2, HVLT-R score, BACS score, change in social functioning, and cortisol. Because the sample size of participants who provided baseline cortisol was smaller than the sample used to develop the original risk calculator and to ensure validation and replicability of the five-factor risk calculator before adding cortisol, this model was first validated in the smaller subset of NAPLS2 participants who provided baseline cortisol samples. Baseline cortisol levels were then added to the model to determine risk of conversion.

The original risk calculator model was internally validated with 1000 bootstrap resamples. Although the original model has already been validated in an external sample and validity has been established (Carrión et al., 2016), in the present study, the models were evaluated with and without the same bootstrapping method for consistency. To evaluate performance of the models, Harrell's C-index was used to quantify the ability to discriminate between converters and non-converters. The C-index is similar to the area under the curve for receiver operating characteristics and is optimized for censored data. Values range from 0.5 (no discrimination) to 1.0 (perfect discrimination) (Uno et al., 2011). All statistical analyses were performed using R (R Core Team, 2018).

Results

A total of 417 participants from the NAPLS2 study provided samples for baseline cortisol and had data available for calculating predicted risk of conversion. This subsample did not differ from the original NAPLS2 risk calculator sample on age, gender, race or years of education (see Table 1). Of these, 54 participants converted to psychosis within the two-year study period. Baseline cortisol levels (i.e., cortisol values representing the residuals from a linear regression removing the variance associated with time of sampling) differed between converters (mean = 0.035, SD = 0.12) and non-converters (mean = −0.006, SD = 0.10) ($t(65.8) = -2.48$, p-value = 0.02). A one-way ANOVA showed a significant difference in baseline cortisol between sites ($F(7, 409) = 2.17$, $p = .04$); however, after implementing Bonferroni's correction for multiple comparisons, we did not find any significant pairwise

comparisons in baseline cortisol across the eight sites. Results from the pruned multivariate models are provided in Table 2 in addition to statistics regarding the decrement in C-index for each variable removed from the full model, and the increase for each variable added to the base model. In the sample of 417 participants, the five-variable risk calculator model achieved a C-index of 0.76 (SE = 0.028). At the univariate level, cortisol was found to predict conversion to psychosis (C-index = 0.59, SE = 0.04, hazard ratio = 21.5, *p*-value = 0.004). When cortisol was included in the pruned model of the risk calculator, the model achieved a C-index of 0.781 (SE = 0.028). This represents an increase of 7% in discriminability between converters and non-converters as compared to the original eight-variable risk calculator. For comparison, the results of the unpruned multivariate models are presented in Table 2. In this model, when cortisol was added to the full risk calculator model, the model achieved a C-index of 0.794 (SE = 0.025). The performance of each of the multivariate models is plotted in Figure 1. The hazard ratios and significance levels for each of the terms in the models as well as the C-indices did not change with the inclusion of internal validation with 1000 bootstrap resamples.

Discussion

The purpose of this proof-of-concept study was to investigate whether integrating a measure of baseline cortisol into the existing NAPLS2 risk calculator would improve the accuracy of predicting who does and does not convert to psychosis from the clinical high-risk state over a two-year follow-up period while also increasing the utility of the risk calculator tool. In a subset of NAPLS2 participants, using a multivariate Cox regression, we found that the incorporation of baseline cortisol in a pruned version of the risk calculator showed a 7% improvement in predictive accuracy as compared to the existing risk calculator model and achieved a C-index of 0.781. This also represented a 2% increase in predictive accuracy as compared to the pruned model without cortisol. While most existing predictive models are comprised of solely clinical measures, this is the first study to demonstrate comparable or even improved performance in prediction accuracy by incorporating a biomarker into a clinically based risk calculator. We previously tested whether brain-age gap similarly improved prediction accuracy in the NAPLS2 risk calculator; however, this resulted in only a 1% increase in predictive accuracy from the base model (Chung et al., 2019). The hazard ratio for baseline cortisol (standardized and residualized for time of day of sampling) in the six-factor model was 17.5 ($p = 0.01$), indicating that for each 1 standard deviation increase in cortisol, risk for psychosis increased by 17.5 times. As this is the first study to demonstrate improvement of the risk calculator with the inclusion of a biomarker, it will be important to replicate the findings in an external sample.

The incorporation of baseline cortisol in the risk calculator tool may provide a more nuanced understanding of individual risk for conversion to psychosis from the clinical high-risk state. Within the framework of the neural diathesis-stress model, our findings support the growing body of evidence suggesting that HPA axis functioning may differ for those at risk for converting to psychosis, as expressed through baseline cortisol (Pruessner et al., 2017). While this model is compelling and useful to help understand the role of stress in the development and progression of psychotic disorders, there is still room to further develop our understanding of the complex interaction between genetic risk, environmental factors,

neural substrates of stress, and HPA axis functioning in individuals at risk for developing psychosis. Further, previous research indicates that various indices of HPA activity (e g., basal cortisol, the cortisol awakening response, stress-induced cortisol changes) are independent and measure different aspects of HPA function (Pruessner et al., 2017). Thus, studies examining other measures of HPA axis functioning in the CHR-P population, such as the cortisol awakening response, cortisol response to laboratory stressors, and changes in these measures of cortisol across time, have shown more mixed results in finding differences between CHR-P samples and healthy controls, and between converters and non-converters in CHR-P samples (Pruessner et al., 2017), warranting additional study to further our understanding of the role of the HPA axis in the development of psychotic disorders. In examining the relationship of cortisol levels to stressful life events and total traumas (two variables pruned from the original model), it was found that cortisol was not correlated with stressful life events (r = .07, $p = .14$) or total traumas (r = −.03, $p = .55$). This supports the idea that an underlying HPA axis hypersensitivity as reflected in basal cortisol may be important in distinguishing converts from nonconverters above and beyond the influence that cumulative stress exposure.

HPA-axis dysfunction has been implicated in other forms of psychopathology, including depression and post-traumatic stress disorder (PTSD) (Stetler and Miller, 2011). While psychotic disorders may show a slightly altered pattern of cortisol response involved the cortisol awakening response (CAR) as compared to other forms of psychopathology, more research is needed to better understand the specificity of HPA-axis dysfunction in the CHR-P population as compared to other forms of psychopathology (Borges et al., 2013). Thus, comorbidity with other mood or anxiety disorders in the CHR-P population may also affect cortisol levels. In the sample used for this study, approximately half of the individuals who eventually transitioned to psychosis also met criteria for either depression or PTSD (n = 27), but baseline cortisol levels did not differ between converters with comorbid depression or PTSD and converters without comorbidities ($t(48.2) = -1.04$, $p = 0.3$). Additional research examining the different mechanisms of HPA-axis functioning (e.g., cortisol awakening response and stress-induced cortisol changes) in addition to baseline cortisol in the CHR-P population may elucidate specificity to this population even when accounting for comorbidities.

The potential utility of including baseline cortisol in the risk calculator model extends beyond increasing the overall predictive accuracy. The inclusion of more objective biological measures—in addition to clinical measures—increases the likelihood of a valid and replicable risk assessment for a given individual. Accurate and precise risk assessment measures have implications for treatment decisions in the context of a clinical staging model (Addington et al., 2019). Understanding the likelihood of an individual’s eventual outcome may ultimately allow clinicians to recommend more intensive interventions for those at greatest risk while making different recommendations, perhaps for less intensive interventions, for those at lower risk. Further, drug development and approval by the FDA for pharmacologic interventions in the CHR-P period is more probable with the inclusion of objectively assessed biomarkers, greatly increasing the scope of utility for the risk calculator. Baseline cortisol is a promising candidate for this purpose, as indicated in this study.

The improved risk calculator model could also contribute to better-informed decisions regarding intervention during the clinical high-risk period wherein individual levels of risk may correspond to differential success with either psychosocial or medication-based treatments. Examining the individual components that make up the risk score for a given individual could also be informative in formulating plans for intervention. For example, a recent review of longitudinal pre/post studies of the effects of psychotropics on HPA function concludes that the administration of antipsychotic medications reduces basal cortisol in diagnosed psychotic patients and healthy controls (Subramaniam et al., 2019). Further, the review yielded evidence that patients with higher pre-treatment levels of cortisol are more treatment-responsive, as indexed by symptom reduction. While there are no published longitudinal studies of antipsychotic-cortisol interactions in CHR-P samples, one cross-sectional study showed that baseline cortisol was significantly higher in medication-free CHR-P patients when compared to both healthy controls and CHR patients taking either SSRIs or second-generation antipsychotics (Sugranyes et al., 2012). Thus, further research is warranted to determine whether treatment response, particularly the response to antipsychotics, can be predicted by individual differences in the components that make up the risk score for a given individual. This could be informative in formulating plans for intervention.

As improved risk prediction could have implications for informing treatment decisions for CHR-P individuals (e.g., individuals at higher risk receiving more intensive interventions than those at lower risk), further research is needed to understand what kinds of treatments would be most beneficial for those at highest risk. Age may also play a role in this decision, as baseline cortisol levels have been shown to increase with age through maturational processes for both CHR-P individuals and healthy controls (Walker et al., 2013). In this sample, age was significantly correlated with baseline cortisol levels ($R^2 = 0.14$, $p = 0.006$), which is to be expected given the effect of maturational processes on cortisol levels, although this effect may be amplified in converters as compared to non-converters (Cullen et al., 2020) and thus further investigation on the effect of age is warranted.

Given the sensitivity of the diurnal baseline cortisol measure, it will be important to replicate these findings with a narrower range for time of onset for the first cortisol sample. For eventual clinical applicability, it will be necessary to refine this sampling window so time would not need to be included as a covariate. It will also be necessary to replicate this finding in a sample where site differences can be accounted for statistically. While we did not find any between-site differences in levels of baseline cortisol, the sample was not sufficiently powered to include site as a covariate in our models. In addition, country-specific and cultural factors may contribute to differences in cortisol levels among matched individuals, which could affect the generalizability of this finding and would need to be explored further in the context of a CHR-P sample (Souza-Talarico et al., 2014).

Incorporating an inexpensive and non-invasive biomarker into a risk calculator with good performance shows promise for eventual clinical utility. It will also be important to understand how this model predicts functional outcomes in addition to conversion. Given that the majority of CHR-P individuals do not convert to psychosis, this and other similar models may also help us to understand trajectories for those who do not convert to psychosis

but remain functionally impaired. Risk profiles are heterogeneous and may correspond to heterogeneous trajectories and differences in pharmacologic and psychotherapeutic treatment response; it will be important to continue to refine our prediction models and risk calculators while maintaining ease-of-use and clinical interpretability. In line with best practice for data-driven approaches to prediction, this model should be validated in an external sample—ideally a large, international sample—to ensure replication as there are many factors that affect baseline cortisol.

Acknowledgments

Role of Funding Sources

This work was supported by grants from the National Institutes of Health (T.D.C., grant number U01 MH081902; C.E.B., grant number P50 MH066286; B.A.C., grant number U01 MH081857; S.W.W., grant number U01 MH82022; J.A., grant number U01 MH066134; K.S.C., grant number U01 MH081944; D.O.P., grant number R01 U01 MH066069; D.H.M., grant number R01 MH076989; L.J.S., grant number U01 MH081928, and E.F.W., grant number U01 MH081988).

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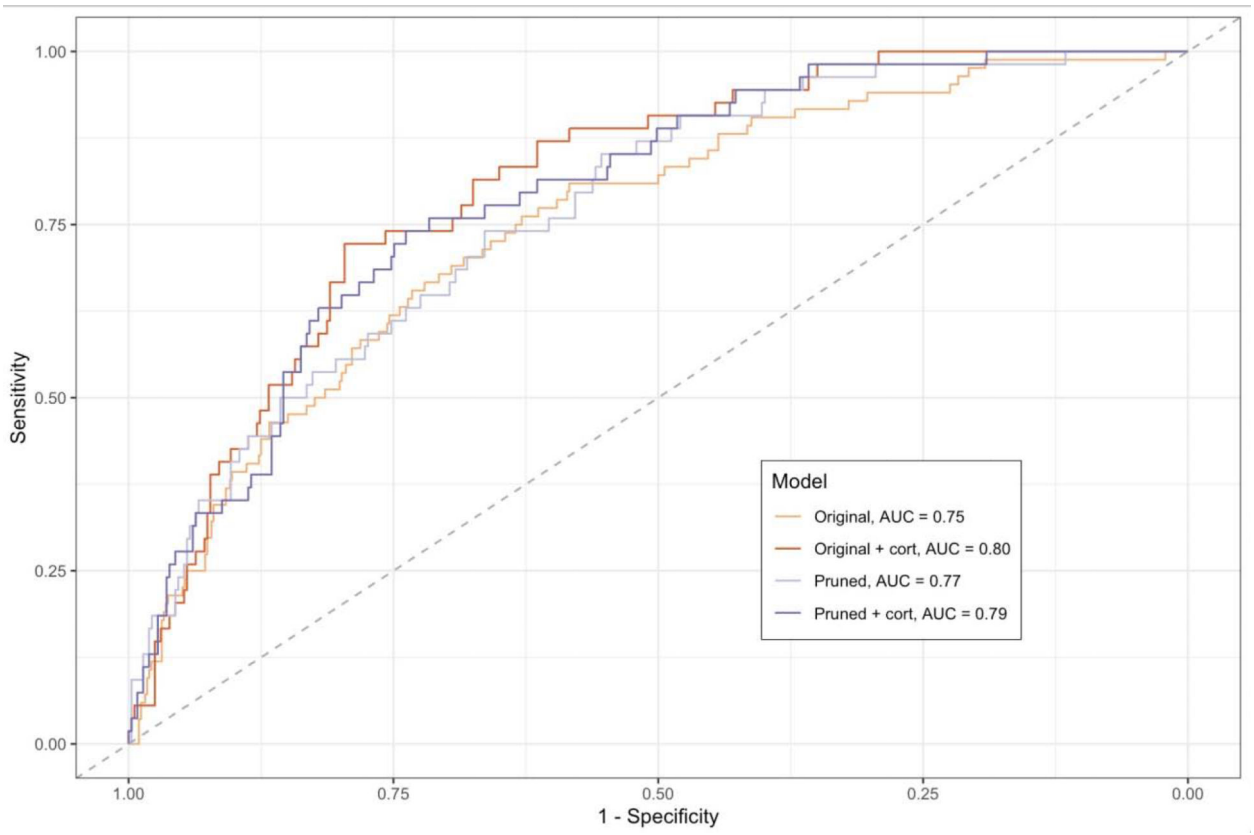

Figure 1.

Performance of multivariate models with and without the inclusion of cortisol

[a]AUC = Area under the curve, calculated by first obtaining predicted risk of conversion from the Cox proportional hazards models, using the mean predicted risk score as the cutoff threshold, and then comparing predicted conversion with actual conversion.

Table 1.

Demographics for the original NAPLS2 risk calculator sample and the subsample of NAPLS2 participants who provided cortisol samples

	Original Sample		Cortisol Sample		Test statistic	*p*-value
	n		*n*		$t/X^2(df)$	
Age, mean (SD)	596	18.5 (4.3)	417	18.7 (4.4)	$t(879.5) = -0.52$	0.60
Women, No. (%)	596	252 (42.2)	417	180 (43.2)	$X^2(1) = 0.078$	0.78
Race						
White, No. (%)	596	345 (57.9)	417	236 (56.6)	$X^2(3) = 0.58$	0.92
Black		91 (15.3)		70 (16.8)		
Asian		47 (7.9)		34 (8.2)		
Other		113 (19.0)		77 (18.5)		
Education (years), mean (SD)	595	11.3 (2.8)	416	11.3 (2.8)	$t(888.7) = -0.03$	0.97

Table 2.

Statistics for Variables in Multivariate Cox Proportional Hazards Regression Analysis of Conversion to Psychosis[a]

	Multivariate model before pruning			C-index[b]		Multivariate model after pruning			C-index	
	HR	95% CI	p	Decrement if removed	Increase if added	HR	95% CI	p	Decrement if removed	Increase if added
Modified SIPS items P1 + P2	1.62	1.36–1.92	<0.001*	0.117	N/A[c]	1.65	1.39–1.95	<0.001*	0.123	N/A[c]
Decline in social functioning	1.23	0.94–1.63	0.14	0.009	0.010	1.22	0.93–1.61	0.15	0.007	0.010
HVLT-R	0.93	0.88–0.98	0.008*	0.017	0.037	0.93	0.88– 0.98	0.008*	0.018	0.037
BACS	0.995	0.97–1.02	0.71	0.001	0.026	0.996	0.97–1.02	0.74	0.001	0.026
Age	0.92	0.85–0.996	0.04*	0.018	0.015	0.94	0.88–1.01	0.10	0.009	0.015
Stressful life events	1.05	0.99–1.10	0.14	0.014	0.004	--	--	--	--	--
Family history	1.20	0.59–2.45	0.61	0.000	0.006	--	--	--	--	--
Total traumas	0.96	0.81–1.14	0.64	0.002	0.009	--	--	--	--	--
Baseline cortisol	15.81	1.66–150.86	0.02*	0.015	0.019	17.51	1.96–156.31	0.01*	0.016	0.019

[a]SIPS = Structured Interview of Prodromal Syndromes; BACS = Brief Assessment of Cognition in Schizophrenia; HVLT-R = Hopkins Verbal Learning Test – Revised; HR = hazard ratio; CI = confidence interval

[b]Harrell's C-index; the C-index for the overall unpruned model was 0.79, the C-index for the overall pruned model was 0.781

[c]base model includes only P1P2, C-index is 0.71