Mediation Analyses of Insight, Quality of Life, Depression, and Suicidality:
Results From the FACE-SZ Cohort

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ABSTRACT

Objective: The relationship between greater insight and increased risk of suicide in patients with schizophrenia is debated. The purpose of this study was to assess whether quality of life (QoL) and depression mediated the association between insight and suicidality.

Methods: Between March 2010 and December 2015, 527 community-dwelling adults with stable schizophrenia according to *DSM-IV* criteria were included in a multicenter cross-sectional study, the FondaMental Academic Centers of Expertise for Schizophrenia (FACE-SZ) Study. Structural equation modeling was used for mediation analyses among insight, QoL, depression, and suicidality, controlling for the global level of schizophrenic symptoms.

Results: The model provided a good fit for the data ($\chi^2_3 = 1.4$, $P = .708$, Tucker-Lewis index = 1, comparative fit index = 1, root mean square error of approximation = 0, standardized root mean square residual = 0.008) and explained 27% of the variance in suicidality. Poorer QoL and greater severity of depression mediated 68.4% of the positive association between insight and suicidality (full mediation). Poorer QoL mediated 48% of the positive effect of insight on depression (partial mediation). The severity of depression mediated 91.2% of the negative relationship between QoL and suicidality (full mediation).

Conclusions: Insight appears to be an indirect risk factor for suicide in patients with schizophrenia, with the link being mediated by poorer QoL and worse underlying depression, mainly by a sequential pathway but also by a less important parallel pathway.

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Poor insight, defined as an impaired awareness of one's illness, has been reported in 50%–75% of patients with schizophrenia.[1,2] Insight has been defined as a multidimensional construct that includes awareness of the mental illness, need for treatment, and social consequences of the illness and the ability to relabel psychotic symptoms and attribute symptoms to the mental disorder.[1,3] Poor insight is associated with negative outcomes such as poor treatment adherence,[4] leading to a higher frequency of readmission,[5] which is more often involuntary.[6] Furthermore, lack of insight is associated with poor functioning.[7,8] Increasing awareness of illness may thus lead to a better outcome.

The insight paradox in schizophrenia describes the fact that better insight seems to be associated with lesser well-being and self-esteem.[9] Suicide is a major issue in schizophrenia,[10] and several studies[11,12] reported that good insight was related to increased suicidality for these patients. In contrast, a recent review[13] has concluded there was little evidence supporting the direct relationship between insight and suicide risk in schizophrenia and suggested a mediating role of depression. However, to our knowledge, no study has validated this hypothesis with structural equation modeling (SEM). Quality of life (QoL), which has been defined as "the gap between a person's expectations and achievements,"[14] may also mediate the association between poor insight and suicide. Poor QoL has been shown to have a significant association with high level of insight[15] and increased suicidality in patients with schizophrenia.[16,17]

The mediation of QoL and depression between insight and suicidality may occur through different pathways. First,

Clinical Points

- Although the relationship between better insight and increased suicide risk in schizophrenia is not well understood, the current study showed this relationship to be fully mediated by depression and quality of life.
- Interventions aiming at insight improvement in schizophrenia should focus on quality of life and depressive symptoms to prevent suicide.

the mediation may be sequential (see Figure 1A), which would imply that poor QoL fully mediates the relationship between insight and depression and that depression fully mediates the relationship between QoL and suicidality. The sequential mediation is compatible with the defense theory of insight,[18] which posits that better insight leads to a more realistic self-assessment, with a greater negativity of judgments, particularly about the social impact of the illness on QoL. The decreased QoL may then induce depression via a demoralization syndrome with hopelessness about the future.[11] A decrease in QoL should precede the occurrence of depression, according to the hypothesis by Birchwood et al[19] that "depression in chronic schizophrenia is in part a psychological response to an apparently uncontrollable life-event, namely the illness and its long term disabilities."[19(p398)] The sequential mediation is also compatible with the negative associations between insight and QoL[20] and between QoL and depression,[21] the positive association between depression and suicidality,[22] and the lack of significant associations between insight and depression[23] and between QoL and suicidality[24] when covariates are taken into account.

The mediation of QoL and depression between insight and suicidality may also be parallel (see Figure 1B): in that case, the relationship between insight and depression would not be mediated by QoL, and depression would not mediate the relationship between QoL and suicidality. The parallel mediation is also compatible with several experimental results showing a significant positive association between insight and depression[9] and between QoL and suicidality.[16,17]

Finally, the mediation of QoL and depression between insight and suicidality may be both sequential and parallel (see the mixed mediation model in Figure 1C), which would imply that a poor QoL partially mediates the relationship between insight and depression and that depression partially mediates the relationship between QoL and suicidality. This mixed mediation is supported by the escape theory of suicide,[25] which predicts that when the QoL is low, the discrepancy between patients' current perceptions of their lives and their expectations prompts a suicidal attempt. According to this theory, the relationship between poor QoL and suicide risk is direct, but also indirect via negative affect, especially depression and anxiety.[25]

Aims of the Study

In this study, by using SEM, we aimed to investigate whether the relationship between insight and suicidality was mediated by poor QoL and severity of depression while controlling for the global level of schizophrenic symptoms. This study also explored whether this mediation occurred through a sequential, a parallel, or a mixed pathway.

METHODS

Study Design and Recruiting Network Characteristics

This multicenter cross-sectional study included patients recruited into the FondaMental Academic Centers of Expertise for Schizophrenia (FACE-SZ) cohort between March 2010 and December 2015 by a French nationwide network of 10 Schizophrenia Expert Centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, and Versailles). This network was set up by the FondaMental Foundation (www.fondation-fondamental.org) and funded by the French Ministries of Research and Health, with the goal of building links between systematic clinical assessment and research.[26]

Participants

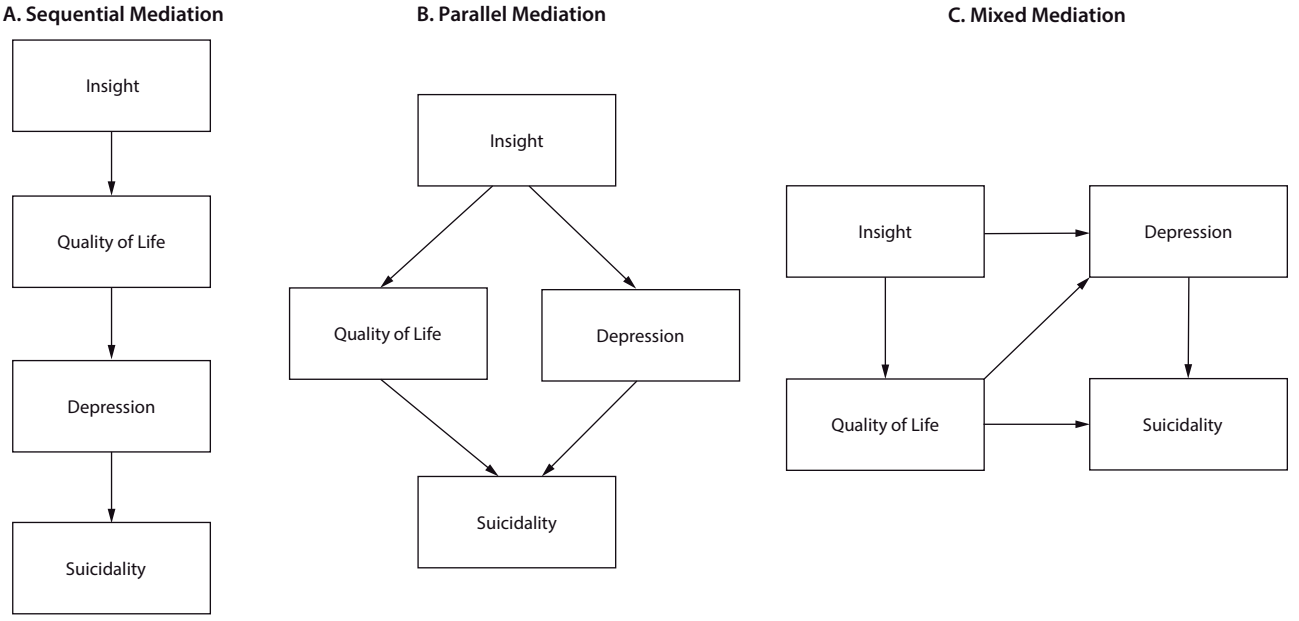
Schizophrenia, schizoaffective disorder, and schizophreniform disorders were diagnosed based on the Structured Clinical Interview for *DSM-IV* Axis I Disorders.[27] Patients were interviewed by senior psychiatrists or psychologists specialized in schizophrenia who were all members of the specialized multidisciplinary teams of the Expert Centers. The study included only patients with clinically stable schizophrenia, defined as no admission or treatment change in the past 4 weeks.

The assessment protocol was approved by the ethics review board (CPP-Ile de France *IX*, January 18, 2010), which required providing all patients with an informational letter but waived the requirement for written informed consent. However, we sought the verbal agreement of every patient before inclusion in the study.

Assessment Tools

The level of schizophrenic symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS),[28] which has an excellent interrater reliability (between 0.83 and 0.87[29]). Insight was assessed using both a self-report scale and a clinician-rated instrument. Although these 2 types of instruments show a moderate to high agreement in schizophrenia,[30,31] using both is recommended to enhance the reliability of insight assessment.[32] The self-report tool was the Birchwood Insight Scale (BIS)[33] (8 items; 3 Likert-scale response levels; higher scores indicate better insight; Cronbach $\alpha = 0.78$[34]). The clinician-rated tool was the abbreviated version of the Scale to Assess Unawareness in Mental Disorder (SUMD), which is rated during a specific interview with a trained clinician (9 items; 3 response levels; higher scores indicate a greater degree of unawareness; Cronbach $\alpha = 0.76–0.83$; interrater reliability = 0.68–1.00).[35,36] QoL was assessed with the Schizophrenia Quality of Life Questionnaire (S-QoL), a self-report scale with 41 items (5 response levels; higher scores indicate better QoL; Cronbach $\alpha = 0.72–0.90$).[37] Current depressive symptoms

Figure 1. Hypothesized Pathways From Insight to Suicidality



were evaluated with the Calgary Depression Scale for Schizophrenia (CDSS),[38] a 9-item structured interview scale (4 response levels; higher scores indicate worse depression; Cronbach α = 0.71–0.78; interrater reliability = 0.9).[39] Scores of 6 or higher are usually taken to indicate depression in patients with schizophrenia.[40] Suicidality was assessed during a clinician interview that explored the patient's experience during the past 12 months. A 6-level ordinal scale ranging from 0 to 5 was used: 0, no death thoughts, suicidal ideation, or suicidal behavior; 1, patient believes life is not worth living; 2, patient has death wishes (eg, wanting to fall asleep in bed and never wake up again); 3, patient has already thought to commit suicide, but knowing she/he would never act; 4, patient has seriously thought about or made plans for committing suicide; 5, patient has attempted suicide.

Statistical Analyses

First, zero-order correlations between each measure were calculated with Pearson correlation coefficients.

To test whether there was a mediation of QoL and depression between insight and suicidality and whether this mediation was serial, parallel, or mixed, SEM with mediation analyses was performed. The SEM model included all possible relationships between variables that are described in the introduction and Figure 1 plus the direct effect of insight on suicidality (see Figure 2 for a representation of all relationships tested in the model). The SEM model thus tested 3 hypotheses simultaneously: (1) poorer QoL and severity of depression mediate the positive association between insight and suicidality, (2) poorer QoL mediates the positive association between insight and depression, and (3) severity of depression mediates the positive association between QoL and suicidality. The PANSS total score was entered as a covariate in the model.

Analyses were performed using the lavaan package[41] of R statistical software with the maximum likelihood estimation method. SEM requires at least 15 participants for each observed variable.[42] We included 6 observed variables in the model and therefore required at least 90 participants. Factor loadings were used to specify associations between the latent variable insight and the indicator variables SUMD and BIS scores. Linear regression analyses were performed to evaluate relationships among the variables and were indexed using standardized path coefficients. We used a nonparametric bootstrapping of the standard error (SE) with 2,000 iterations for the correlation and SEM analyses.

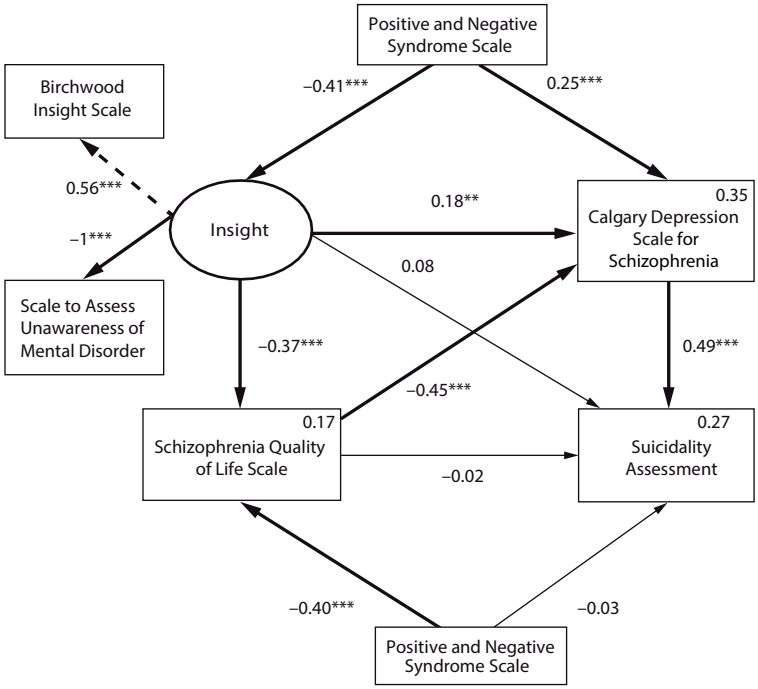
The fit between the model and the data was assessed using 5 indices: the χ^2 goodness-of-fit statistic (χ^2), Tucker-Lewis index (TLI), comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR).

RESULTS

Participants

We included 527 patients. There were 8.9% with missing data, which were handled using the full information maximum likelihood estimation. The 15 patterns of missingness are reported in Supplementary eTable 1, and the covariance coverage matrix of missing data is included in Supplementary eTable 2. Table 1 reports the sociodemographic and clinical characteristics of patients. Cronbach α values of the different measures were satisfactory (BIS: 0.75; SUMD: 0.87; S-QoL: 0.89; CDSS: 0.83; PANSS: 0.89). The mean PANSS total score indicated mild symptoms.[28] The mean insight scores denoted a moderate level of unawareness of the illness. The mean total BIS score was around the cutoff of 9 for impaired insight,[33] and the mean SUMD score on single items was

Figure 2. Mediation Model[a]



[a]The oval represents the unobserved latent variable insight. Rectangles represent observed measured variables. Dashed arrows are drawn between a latent variable and its reference indicator with a corresponding unstandardized regression fixed to a weight of 1 (to fix the unit of measurement of the unobserved variable). Plain arrows are drawn between variables with free regression weight. The values along the plain arrows are standardized path coefficients. The squared multiple correlation (R^2) value for a dependent variable appears inside the corresponding rectangle. Bold arrows are drawn between 2 variables that are significantly associated, whereas thin arrows are drawn between 2 variables that are not significantly associated.
**.01 > P > .001.
***P < .001.

0.6, suggesting slightly impaired awareness of the disease. The mean QoL score indicated intermediate QoL. The CDSS score was ≥ 6 for 29.8% of patients. Finally, 31.2% of patients had attempted suicide in their lifetime. During the past 12 months, 56.7% had no death-related thought, 4.7% believed life was not worth living, 5.5% had death wishes, 17.6% had already thought to commit suicide, 8.7% made plans for committing suicide, and 6.6% attempted suicide.

Structural Equation Modeling and Mediation Analyses

Table 2 reports the zero-order correlations between the indicator variables. All of these correlations were significant except the correlation between PANSS total score and suicidality. Additional correlational analyses between 3 dimensions of the SUMD (awareness of mental disorder, of the consequences of mental disorder, and the effects of medication) are reported in Supplementary eTable 3. The significant relationships between the total SUMD score and the other variables included in the model (QoL, depression, and suicidality) were mainly explained by the significant impact of the awareness of the consequences of mental disorder but not by the 2 other dimensions of the SUMD.

Table 1. Sociodemographic and Clinical Characteristics of the 527 Study Patients

Variable[a]	Mean	SD
Age, y	32.3	9.8
Illness duration, y	10.6	8.1
Total time in hospital, mo	7.6	9.8
BIS score (0–12)	8.8	3.0
SUMD score (0–100)	34.9	27.8
S-QoL score (0–100)	51.8	19.1
CDSS score (0–27)	3.9	4.4
Suicidality[b] (0–5)	1.4	1.7
PANSS		
Positive score (7–49)	14.8	5.8
Negative score (7–49)	20.6	7
General Psychopathology score (16–112)	35.5	10.2
Total score (31–217)	71.0	19.1
Chlorpromazine equivalents, mg/24 h	645.8	592.5
	n	%
Male	389	73.8
Schizoaffective disorder	128	24.3
Schizophreniform disorder	9	0.02
Admission in the past year	208	39.4

[a]The ranges listed are possible ranges for these variables.
[b]Suicidality assessed with a 6-level ordinal scale during clinician interview.
Abbreviations: BIS = Birchwood Insight Scale, CDSS = Calgary Depression Scale for Schizophrenia, PANSS = Positive and Negative Syndrome Scale, S-QoL = Schizophrenia Quality of Life Questionnaire, SUMD = Scale to Assess Unawareness of Mental Disorder.

Table 2. Observed Pairwise Correlation Matrix[a]

	BIS		SUMD		S-QoL		CDSS		Suicidality	
Measure	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value
SUMD	−0.53	<.001								
S-QoL	−0.10	.03	0.22	<.001						
CDSS	0.10	.022	−0.19	<.001	−0.54	<.001				
Suicidality	0.13	.004	−0.19	<.001	−0.31	<.001	0.51	<.001		
Total PANSS score	−0.21	<.001	0.42	<.001	−0.25	<.001	0.29	<.001	0.08	.068

[a]*P* values were computed from standard errors estimated using bootstrapping with 2,000 iterations.
Abbreviations: BIS = Birchwood Insight Scale, CDSS = Calgary Depression Scale for Schizophrenia, PANSS = Positive and Negative Syndrome Scale, S-QoL = Schizophrenia Quality of Life Questionnaire, SUMD = Scale to Assess Unawareness of Mental Disorder.

The model provided a good fit for the data, as suggested by the nonsignificant χ^2 goodness-of-fit statistic ($\chi^2_3 = 1.4$, $P = .708$), TLI and CFI greater than 0.95 (TLI = 1, CFI = 1), RMSEA not significantly larger than 0.05 (RMSEA = 0, 1-sided P value = .935 for the test of the null hypothesis RMSEA = 0.05), and SRMR lower than 0.08 (0.008).

The model explained 27% of the variance in suicidality, BIS and SUMD scores were both reliable and valid indicator variables of the latent variable insight, as supported by the significant moderate-to-high factor loadings (standardized $\beta = 0.56$ and 1, respectively; $P < .001$, Supplementary eTable 4 and Figure 2).

In sum, the analysis revealed the following relationships between the variables (Figure 2): a significant negative association between insight and QoL, a significant negative association between insight and depression, a significant negative association between QoL and depression, and a significant positive association between depression and suicidality. Moreover, the PANSS total score was negatively associated with insight and QoL and positively linked to depression.

The direct effect of insight on suicidality was not significant when QoL and depression were included in the model (standardized $\beta = 0.081$, SE = 0.056, $z = 1.5$, $P = .144$). We found that 68.4% of the total effect of insight on suicidality was mediated by QoL and depression (SE = 0.158, $z = 4.3$, $P < .001$). Direct, indirect, and total effects between insight, QoL, and depression were all significant (Table 3 and Figure 2). We found that 48% of the total effect of insight on depression was mediated by QoL (SE = 0.089, $z = 5.4$, $P < .001$). The direct effect of QoL on suicidality was not significant when depression was included in the model (standardized $\beta = -0.02$, SE = 0.052, $z = -0.4$, $P = .684$). We found that 91.2% of the total effect of QoL on suicidality was mediated by depression (SE = 0.202, $z = 4.5$, $P < .001$).

Several alternative models were tested, as reported in eAppendix 1. The first model included PANSS subcomponents as covariates. The second model measured depression with CDSS total score minus suicide item, as the presence of a suicide item in the CDSS might have led to an overestimation of the relationship between depression and suicidality. The last model measured suicidality with the suicide item of the CDSS, which evaluated the suicide risk during the last 2 weeks. The results achieved with these alternative models were very close to those obtained with the model described here.

DISCUSSION

Here, we used SEM to evaluate whether QoL and depression mediated the relationship between insight and suicidality in schizophrenia. We found that the positive association between good insight and high suicidality was fully mediated by poor QoL and depressive symptoms. A complete mediation of the relationship between insight and suicidality by depression was reported in a recent study.[43] Our model explained only 27% of the variance in suicidality, supporting a role for other factors such as living alone, a recent loss, agitation/restlessness, fear of mental disintegration, poor treatment adherence, and drug misuse.[22]

QoL and depression fully mediated the relationship between insight and suicidality by serial and parallel pathways, thus validating a mixed mediation model. First, QoL partially mediated about half of the association linking insight to depression, but the direct effect of insight on depression remained significant when the effect of QoL was taken into account. This result is not entirely compatible with the defense theory of insight, according to which depression occurs after an improvement of insight because of a more accurate view of the negative impact of the disorder on QoL. This direct association might be ascribable to mediators that were not measured in this study, such as high internalized stigma, hopelessness, low self-esteem, or rumination.[44] Second, the negative association linking QoL to suicidality was fully mediated by depression. This result seems at variance with previous studies of schizophrenia[16,17] in which QoL was associated with suicidality independently from depression. Failure to use specific scales for depression in schizophrenia may have led to inaccuracies in the evaluation of depression in these studies, impairing their ability to detect a mediating role for depression in the association between QoL and suicidality. This result is not entirely compatible with the escape theory of suicide, which postulates that suicide is a consequence of the perception of the negative impact of the disorder on QoL. A low QoL does not seem to be sufficient to the emergence of suicidal thoughts or behaviors in the absence of depression.

Table 3. Statistics for Mediation Analyses Coefficients

	Quality of Life				Depression				Suicidality			
Effect	Standardized β (or Proportion)	SE[a]	*z*	*P* Value	Standardized β (or Proportion)	SE[a]	*z*	*P* Value	Standardized β (or Proportion)	SE[a]	*z*	*P* Value
Direct effects												
Insight	−0.366	0.053	−6.9	<.001	0.178	0.053	3.3	.001	0.081	0.056	1.5	.144
Quality of life					−0.448	0.037	−12.2	<.001	−0.021	0.052	−0.4	.684
Depression									0.490	0.050	9.9	<.001
Indirect[b] effects												
Insight					0.164	0.026	6.4	<.001	0.175	0.032	5.5	<.001
Quality of life									−0.220	0.029	−7.6	<.001
Total[c] effects												
Insight	−0.366	0.053	−6.9	<.001	0.342	0.056	6.1	<.001	0.256	0.060	4.3	<.001
Quality of life					−0.448	0.037	−12.2	<.001	−0.241	0.050	−4.8	<.001
Depression									0.490	0.050	9.9	<.001
Proportion of mediated effect												
Insight					0.480	0.089	5.4	<.001	0.684	0.158	3.5	<.001
Quality of life									0.912	0.202	4.5	<.001

[a]Standard errors were estimated using model-based bootstrapping with 2,000 iterations.
[b]The indirect effect of insight on suicidality includes all possible indirect paths from insight to suicidality (the path mediated by quality of life alone, the path mediated by depression alone, and the path mediated by both depression and quality of life).
[c]The total effect of insight on suicidality also includes all possible paths from insight to suicidality.

The levels of insight in our study were consistent with those found in a previous study[33] with patients having recovered from an acute episode of schizophrenia. The lifetime prevalence of suicidal attempts in the present study was within the range found in previous studies.[45] Mean QoL scores were similar to those in an earlier study from France.[46] The prevalence of depression was close to the 40% value reported in another study.[47] These consistencies support the general applicability of our findings to patients with stable schizophrenia, using the same instruments as were included in the current study.

Limitations of our study include the cross-sectional design, which precludes the evaluation of causality and direction of potential causal links. For instance, should the association linking insight to depression indicate causality, one hypothesis is that insight increases the tendency toward depression. Another is that depression leads the individual with schizophrenia to be more pessimistic, and thus realistic, about the illness and its social impact, ie, to acquire insight (the depressive realism model).[18] A previous study[48] has suggested that a history of suicide attempts would lead to better insight in schizophrenia, as suicide attempters may be more likely to acknowledge that they have a mental illness. Moreover, the relationship found between QoL and depression might be interpreted in the direction of depressive symptoms' causing a poor QoL. Longitudinal studies would help to distinguish between the different directions of causality, using, for example, the methodology of cross-lagged effects. Another limitation is our use of a nonvalidated tool to assess suicidality: further studies should evaluate suicidality with a validated scale. Moreover, we did not distinguish between suicidal ideation and behaviors, which might involve different mechanisms and risk factors.[17,24] The exclusion of patients with completed suicide and admitted patients may have biased the recruitment toward patients with a low risk of suicide. As raters were not blinded to each variable in this cross-sectional study, a potential bias could have been introduced when evaluating the relationships among insight, QoL, depression, and suicidality.

Our findings have important implications for future clinical studies. Psychoeducational programs seek to improve insight and are widely recommended for patients with schizophrenia.[49] Our results suggest that an accurate evaluation of depressive symptoms should be routinely performed in psychoeducational interventions for patients with schizophrenia. Emphasis should be placed on differentiating negative and depressive symptoms, as the association with suicide is far weaker for negative symptoms than for depression[50]; specific tools such as the CDSS may be especially useful for making this distinction. Our findings also suggest that psychoeducational programs should include modules focusing specifically on QoL and depressive symptoms to avoid increasing suicidality. Depression in schizophrenia often goes untreated, and efficient pharmacologic, psychotherapeutic, and psychosocial treatment of depression in patients with schizophrenia should be developed.

In conclusion, our study supports a link between insight and suicidality but indicates that other variables mediate this link. This study is a first step to validate a pathway from better insight to worse QoL, from worse QoL to worse depression, and, finally, to an increased suicide risk. Thus, our study sheds light on the mechanisms that might explain suicidality in patients with schizophrenia and good insight.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Mediation Analyses of Insight, Quality of Life, Depression and Suicidality: Results From the FACE-Schizophrenia Cohort

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1. **eTable 1** Patterns of missingness of variables included in the model
2. **eTable 2** Covariance coverage matrix of missing data for the variables included in the model
3. **eTable 3** Pearson correlations between the three dimensions of the SUMD and the other variables included in the model
4. **eTable 4** Statistics for the estimated factor loadings and standardized path coefficients
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Supplementary eTable 1. Patterns of missingness of variables included in the model

Birchwood Insight Scale	Scale to assess Unawareness of Mental Disorder	Schizophrenia Quality of Life	Calgary Depression Scale	Suicidality	Total Positive and Negative Syndrome Scale score
available	available	available	available	available	available
available	missing	available	available	available	available
missing	available	available	available	available	available
missing	available	missing	available	available	available
missing	missing	available	available	available	available
available	available	missing	available	available	available
available	available	available	available	available	missing
available	missing	available	missing	available	missing
missing	missing	missing	available	available	available
available	missing	available	available	available	missing
available	missing	missing	available	available	available
available	missing	available	missing	available	available
available	available	missing	missing	available	available
available	available	available	missing	available	missing
available	available	available	missing	available	available

Supplementary eTable 2. Covariance coverage matrix of missing data for the variables included in the model

Covariance coverage is the proportion of complete cases for each variable individually (on the diagonal) and variable pairs (below the diagonal).

	Birchwood Insight Scale	Scale to assess Unawareness of Mental Disorder	Quality of Life in Schizophrenia	Calgary Depression Scale	Suicidality	Total Positive and Negative Syndrome Scale score
Birchwood Insight Scale	0.86					
Scale to assess Unawareness of Mental Disorder	0.59	0.70				
Schizophrenia Quality of Life	0.84	0.65	0.94			
Calgary Depression Scale	0.84	0.70	0.93	0.99		
Suicidality	0.86	0.70	0.94	0.99	1	
Total Positive and Negative Syndrome Scale score	0.84	0.69	0.92	0.97	0.98	0.98

Supplementary eTable 3. Pearson correlations between the three dimensions of the SUMD and the other variables included in the model:

	SUMD - Awareness of Mental Disorder		SUMD - Awareness of the Consequences of Mental Disorder		SUMD - Awareness of the Effects of Medication	
	r	*P* value	r	*P* value	r	*P* value
BIS	-0.56	<0.001	-0.49	<0.001	-0.50	<0.001
S-QoL	0.09	0.068	0.15	0.005	-0.03	0.654
CDS	-0.08	0.146	-0.14	0.005	0.07	0.226
Suicidality	-0.09	0.068	-0.15	0.002	0.06	0.297
Total PANSS score	0.3	<0.001	0.35	<0.001	0.26	<0.001

BIS: Birchwood Insight Scale; SUMD: Scale to assess Unawareness of Mental Disorder; S-QoL: Quality of Life in Schizophrenia; CDS: Calgary Depression Scale; PANSS: Positive and Negative Syndrome Scale
P-values were computed from standard errors estimated using bootstrap with 2000 iterations.

Supplementary eTable 4. Statistics for the estimated factor loadings and standardized path coefficients

	Variables	Estimate	Standard Error[a]	z	*P* value
Factor loading	Insight -> Birchwood Insight Scale	0.56	0.05	11.4	<0.001
	Insight -> Scale to assess Unawareness of Mental Disorder	-1	0.07	-14.9	<0.001
Standardized path coefficients	Insight -> Quality of Life	-0.37	0.05	-6.9	<0.001
	Insight -> Calgary Depression Scale	0.18	0.05	3.3	0.001
	Quality of Life -> Calgary Depression Scale	-0.45	0.04	-12.2	<0.001
	Insight -> Suicidality	0.08	0.06	1.5	0.144
	Quality of Life -> Suicidality	-0.02	0.05	-0.4	0.684
	Calgary Depression Scale -> Suicidality	0.49	0.05	9.9	<0.001
	Positive and Negative Syndrome Scale -> Insight	-0.41	0.05	-8.9	<0.001
	Total Positive and Negative Syndrome Scale score -> Quality of Life	-0.4	0.05	-8.2	<0.001
	Positive and Negative Syndrome Scale -> Calgary Depression Scale	0.25	0.04	5.7	<0.001
	Positive and Negative Syndrome Scale -> Suicidality	-0.03	0.05	-0.6	0.579

[a]Standard errors were estimated using model-based bootstrapping with 2000 iterations.

eAppendix 1. Several alternative Structural Equations Models (SEM) tested to assess the reliability of the results obtained with the model presented in the main manuscript.

MODEL INCLUDING THE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) SUBCOMPONENTS AS COVARIATES

Principal component analysis (PCA) of the PANSS

The data set for the PCA included the 30 items of the PANSS. Horn's parallel analysis[1] determined the number of components to be extracted in the PCA. This method contrasts eigenvalues produced through a parallel PCA on 1000 random datasets, with the same number of variables and observations as the observational dataset, to generate eigenvalues for components that are adjusted for sample error-induced inflation. Adjusted eigenvalues > 1 indicate dimensions to retain. A varimax rotation followed the PCA. The rotation was performed to simplify the component structure. In PCA, the usual standard for sample size is a participant-to-variable ratio > 5[2], and therefore required 150 participants for the current study.

Horn's parallel analysis showed that five components should be retained, as their adjusted eigenvalue was above 1 (see the table below).

Component	Adjusted Eigenvalue	Unadjusted Eigenvalue
1	**7.13**	**7.60**
2	**2.87**	**3.28**
3	**1.87**	**2.23**
4	**1.14**	**1.46**
5	**1.14**	**1.42**
6	0.86	1.11
7	0.77	0.98
8	0.77	0.96
9	0.69	0.84
10	0.66	0.78
11	0.68	0.78
12	0.66	0.73
13	0.64	0.68
14	0.61	0.63
15	0.63	0.63
16	0.60	0.58
17	0.60	0.54
18	0.58	0.50
19	0.58	0.48
20	0.59	0.47
21	0.60	0.45
22	0.57	0.40
23	0.58	0.39
24	0.58	0.37
25	0.58	0.34
26	0.58	0.31
27	0.59	0.29
28	0.60	0.28
29	0.60	0.25
30	0.63	0.24

The 5-component structure explained 53% of the variance (see the table below).

	PANSS Negative Component	PANSS Disorganization Component	PANSS Positive Component	PANSS Excitement Component	PANSS Depression Component
Sum of squared loadings	4.66	3.17	2.9	2.75	2.5
Proportion of explained variance	0.16	0.11	0.1	0.09	0.08
Cumulative proportion of explained variance	0.16	0.26	0.36	0.45	0.53

All component loadings were greater than 0.35, and all communalities were higher than 0.2 (see the Table below).

PANSS Item	PANSS Negative Component	PANSS Disorganization Component	PANSS Positive Component	PANSS Excitement Component	PANSS Depression Component	Communality
N1 Blunted affect	**0.80**	0.06	0.04	0.01	0.05	0.65
N3 Poor rapport	**0.78**	0.19	0	0.20	-0.14	0.71
N6 Lack of spontaneity	**0.76**	0.30	-0.07	0.04	-0.09	0.69
N2 Emotional withdrawal	**0.76**	0.03	0.15	0.10	0.12	0.62
N4 Apathetic social withdrawal	**0.66**	0.10	0.10	0.05	0.21	0.50
G7 Motor retardation	**0.62**	0.16	-0.02	-0.13	0.25	0.50
G16 Active social avoidance	**0.52**	0.12	0.06	0.18	0.46	0.53
G13 Disturbance of volition	**0.51**	0.46	0.06	0.15	0.18	0.53
G12 Lack of judgment and insight	**0.36**	0.23	0.28	0.32	-0.34	0.48
G11 Poor attention	0.05	**0.66**	0.14	0.11	0.09	0.48
P2 Conceptual disorganization	0.19	**0.62**	0.35	0.22	-0.09	0.60
N5 Difficulty in abstraction	0.20	**0.61**	0.05	-0.04	-0.08	0.43
N7 Stereotyped thinking	0.29	**0.56**	0.29	0.19	-0.05	0.52
G10 Disorientation	0.07	**0.55**	-0.02	0.12	0.23	0.37
G5 Mannerism	0.35	**0.41**	0.11	0.13	-0.01	0.32
G15 Preoccupation	0.33	**0.41**	0.18	0.4	0.24	0.53
P1 Delusions	0.03	0.15	**0.86**	0.08	0.08	0.78
P3 Hallucinations	-0.04	0.25	**0.63**	-0.04	0.12	0.48
G9 Unusual thought content	0.04	0.45	**0.61**	0.25	0.09	0.65
P6 Suspiciousness	0.19	-0.08	**0.57**	0.40	0.15	0.55
P5 Grandiosity	0	0.07	**0.55**	0.33	-0.13	0.43
G1 Somatic concern	0.11	0.04	**0.40**	0.06	0.23	0.23
P7 Hostility	0.14	0.02	0.23	**0.75**	0.04	0.63
G8 Uncooperativeness	0.34	0.12	0.02	**0.69**	0	0.61
G14 Poor impulse control	-0.04	0.26	0.14	**0.61**	0.13	0.48
P4 Excitement	-0.34	0.27	0.27	**0.53**	-0.02	0.54
G2 Anxiety	0.05	0.12	0.07	0.13	**0.76**	0.62
G6 Depression	0.26	-0.01	0.05	-0.03	**0.72**	0.59
G3 Guilt	0.02	-0.05	0.22	-0.06	**0.55**	0.36
G4 Tension	0.02	0.31	-0.03	0.43	**0.55**	0.58

We obtained components that were very close to the one usually found in schizophrenia[3]. The first component consisted of blunted affect, poor rapport, lack of spontaneity, emotional withdrawal, apathetic social withdrawal, motor retardation, active social avoidance and disturbance of volition. It was designated “Negative Component.” The second component bundled poor attention, conceptual disorganization, difficulty in abstraction, stereotyped thinking, disorientation, mannerism, and preoccupation. It was designated “Disorganization Component.” The third component included delusions, hallucinations, unusual thought content, suspiciousness, grandiosity and somatic concern. It was designated “Positive Component.” The fourth component consisted of hostility, uncooperativeness, poor impulse control, excitement, and was designated "Excitement Component.” The final component included anxiety, depression, guilt, and tension, and was designated “Depression Component.”

SEM and mediation analyses

First, zero-order correlations between the negative, disorganization, positive and excitement component scores in one hand, and the scores on the Birchwood Insight Scale (BIS), the Scale to assess Unawareness of Mental Disorder (SUMD), the Schizophrenia Quality of Life Questionnaire (S-QoL), the Calgary Depression Rating Scale (CDS), and the suicidality on the other hand were calculated with Pearson's correlation coefficients. The results are presented in the table below.

	BIS		**SUMD**		**S-QoL**		**CDS**		**Suicidality**	
	r	p	r	p	r	p	r	p	r	p
PANSS Positive	-0.19	<0.001	0.26	<0.001	-0.23	<0.001	0.19	<0.001	-0.02	0.625
PANSS Negative	-0.12	0.021	0.26	<0.001	-0.11	0.016	0.06	0.201	0.08	0.067
PANSS Disorganization	-0.07	0.149	0.28	<0.001	0.1	0.020	-0.06	0.196	-0.11	0.006
PANSS Excitement	-0.20	<0.001	0.30	<0.001	0.06	0.155	-0.05	0.251	0.03	0.601

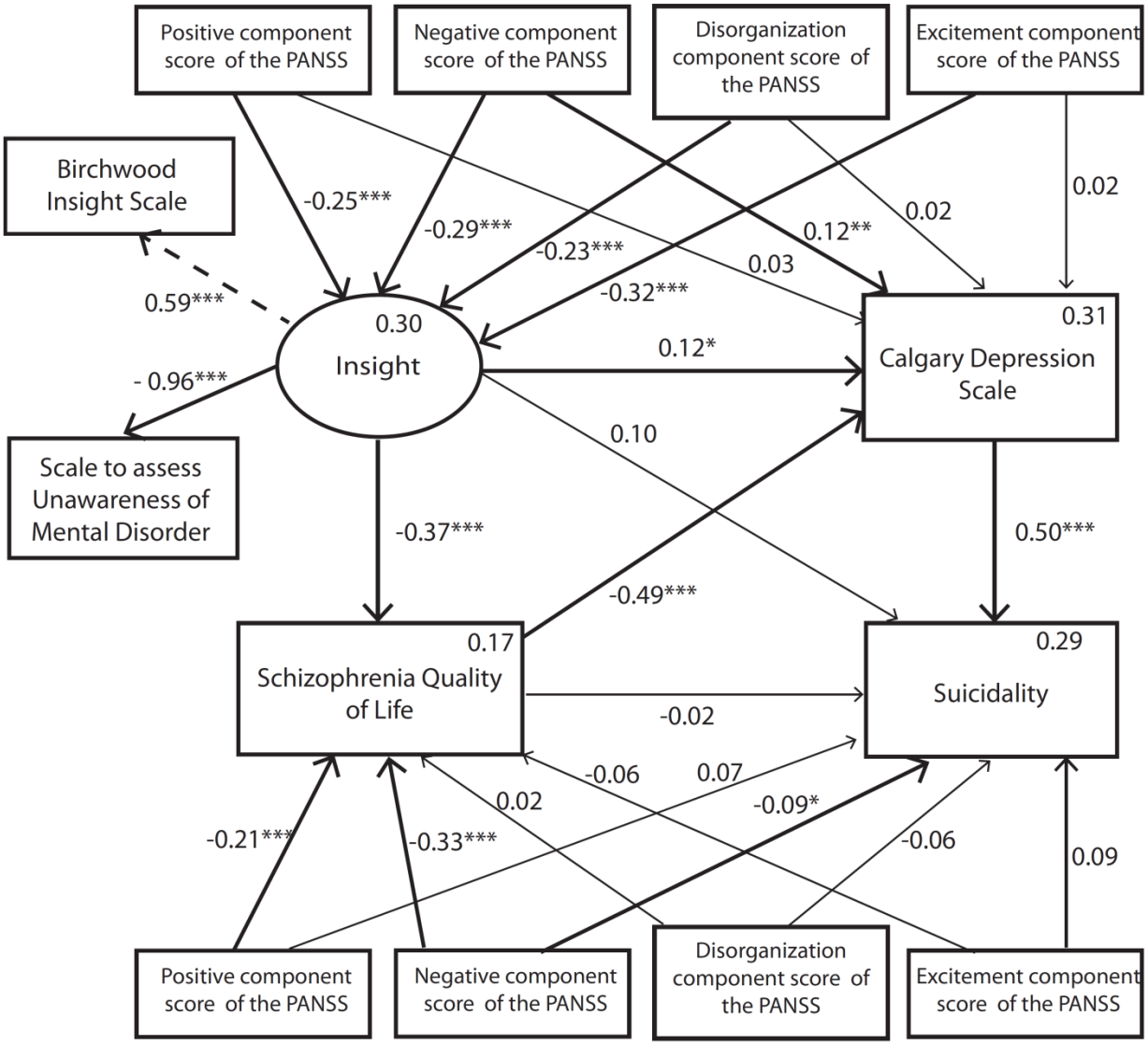
P-values were computed from standard errors estimated using bootstrap with 2000 iterations.

The insight measured with the BIS decreased with higher positive, negative and excitement symptoms. The insight measured with the SUMD decreased with higher positive, negative, disorganization and excitement symptoms. The QoL decreased with higher positive and negative symptoms and increased with higher disorganization symptoms. The depression measured with CDS increased with higher positive symptoms. Finally, the suicidality decreased with higher disorganization symptoms.

We then performed a SEM with mediation analyses, including all the relationships described in the model presented in the main manuscript. The Positive, Negative, Disorganization and Excitement component scores of the PANSS were entered as a covariate in the model, instead of the PANSS total score like in the model presented in the main manuscript. We did not include the PANSS depression component score, as it was redundant with the depression measured with the CDS: the introduction of this covariate would have led to a neutralization of the relationships between depression and the other

variables. We used a nonparametric bootstrapping of the standard errors with 2000 iterations for the correlation and SEM analyses.

The model provided a good fit for the data, as suggested by the nonsignificant chi-square goodness-of-fit statistic ($X^2(6)=4.5$, $P=0.609$), TLI and CFI greater than 0.95 (TLI=1, CFI=1), RMSEA not significantly larger than 0.05 (RMSEA=0, 1-sided P value=0.959 for the null hypothesis RMSEA=0.05), and SRMR lower than 0.08 (0.01). The model explained 29% of the variance in suicidality. The relationships between the variables are presented in the Figure below.



The circle represents the unobserved latent variable insight. Rectangles represent observed measured variables. Dashed arrows are drawn between a latent variable and its reference indicator with a corresponding unstandardized regression fixed to a weight of 1 (to fix the unit of measurement of each unobserved variable). Plain arrows are drawn between variables with free regression weight. The values along the plain arrow are standardized path coefficients. The squared multiple correlation (R^2) value for a dependent variable appears inside the corresponding circle or rectangle. Bold arrows are drawn between two variables that are significantly associated, whereas thin arrows are drawn between two variables that are not significantly associated. **0.01>p>0.001, ***p<0.001.

We found a significant negative association between insight and QoL, a significant negative association between insight and depression; a significant negative association between QoL and depression; and a significant positive association between depression and suicidality. The Positive component score of the PANSS score was negatively associated with insight and QoL. The Negative component score of the PANSS score was negatively related to insight, QoL, and suicidality and positively linked to depression. The Disorganization component score of the PANSS score was negatively related to insight. The Excitement component score of the PANSS score was negatively associated with insight. The statistics for the estimated factor loadings and standardized path coefficients are reported in the table below.

	Variables	**Estimate**	**Standard Error[a]**	**z**	**p**
Factor loading	Insight => Birchwood Insight Scale	0.59	0.05	12.1	<0.001
	Insight => Scale to assess Unawareness of Mental Disorder	-0.96	0.06	-16.9	<0.001
Standardized path coefficients	Insight => Schizophrenia Quality of Life	-0.37	0.06	-6.1	<0.001
	Insight => Calgary Depression Scale	0.12	0.06	2	0.047
	Schizophrenia Quality of Life => Calgary Depression Scale	-0.49	0.04	-13.9	<0.001
	Insight => Suicidality	0.10	0.06	1.6	0.106
	Schizophrenia Quality of Life => Suicidality	-0.02	0.05	-0.4	0.715
	Calgary Depression Scale => Suicidality	0.50	0.05	10.5	<0.001
	PANSS Positive component score => Insight	-0.25	0.04	-5.7	<0.001
	PANSS Negative component score => Insight	-0.29	0.05	-5.8	<0.001
	PANSS Disorganization component score => Insight	-0.23	0.05	-4.8	<0.001
	PANSS Excitement component score => Insight	-0.32	0.05	-6.8	<0.001
	PANSS Positive component score => Schizophrenia Quality of Life	-0.21	0.05	-4.4	<0.001
	PANSS Negative component score => Schizophrenia Quality of Life	-0.33	0.04	-7.4	<0.001
	PANSS Disorganization component score => Schizophrenia Quality of Life	0.02	0.04	0.4	0.685
	PANSS Excitement component score => Schizophrenia Quality of Life	-0.06	0.05	-1.2	0.229
	PANSS Positive component score => Calgary Depression Scale	0.03	0.04	0.7	0.456
	PANSS Negative component score => Calgary Depression Scale	0.12	0.04	2.8	0.005
	PANSS Disorganization component score => Calgary Depression Scale	0.02	0.04	0.4	0.687
	PANSS Excitement component score => Calgary Depression Scale	0.02	0.04	0.4	0.711
	PANSS Positive component score => Suicidality	0.07	0.04	1.7	0.085
	PANSS Negative component score => Suicidality	-0.09	0.04	-2.1	0.034
	PANSS Disorganization component score => Suicidality	-0.06	0.04	-1.5	0.137
	PANSS Excitement component score => Suicidality	0.09	0.05	1.8	0.072

[a]Standard errors are estimated using model-based bootstrapping with 2000 iterations.

The direct effect of insight on suicidality was not significant when QoL and depression were included in the model (standardized β=0.1, standard error: 0.06, z=1.6, *P*=0.106). We found that 61.5% of the total effect of insight on suicidality was mediated by QoL and depression (standard error: 0.16, z=3.8, *P*<0.001).

Direct, indirect, and total effects between insight, QoL, and depression were all significant. We found that 60% of the total effect of insight on depression was mediated by QoL (standard error: 0.134, z=4.5, *P*<0.001).

The direct effect of QoL on suicidality was not significant when depression was included in the model (standardized β=-0.02, standard error: 0.05, z=-0.4, *P*=0.715). We found that 92.8% of the total effect of

QoL on suicidality was mediated by depression (standard error: 0.185, z=5, *P*<0.001). The statistics for mediation analyses coefficients are reported in the Table below.

	Quality of Life				Depression				Suicidality			
Effect	Standardized β (or proportion)	SE[a]	z	*P* value	Standardized β (or proportion)	SE[a]	z	*P* value	Standardized β (or proportion)	SE[a]	z	*P* value
Direct effects												
Insight	-0.367	0.061	-6.1	<0.001	0.121	0.061	2	0.047	0.098	0.061	1.6	0.106
Quality of Life					-0.492	0.035	-13.9	<0.001	-0.019	0.052	-0.4	0.715
Depression									0.495	0.047	10.5	<0.001
Indirect[b] effects												
Insight					0.181	0.031	5.8	<0.001	0.156	0.035	4.5	<0.001
Quality of Life									-0.244	0.029	-8.4	<0.001
Total[c] effects												
Insight	-0.367	0.061	-6.1	<0.001	0.302	0.064	4.7	<0.001	0.254	0.067	3.8	<0.001
Quality of Life					-0.492	0.035	-13.9	<0.001	-0.263	0.048	-5.4	<0.001
Depression									0.495	0.047	10.5	<0.001
Proportion of mediated effect												
Insight					0.599	0.134	4.5	<0.001	0.615	0.16	3.8	<0.001
Quality of Life									0.928	0.185	5	<0.001

[a] Standard errors were estimated using model-based bootstrapping with 2000 iterations.
[b] The indirect effect of insight on suicidality includes all possible indirect paths from insight to suicidality (the path mediated by quality of life alone, the path mediated by depression alone, and the path mediated both by depression and quality of life).
[c] The total effect of insight on suicidality also includes all possible paths from insight to suicidality.

Conclusions

We conclude that the results were very close to those obtained with the model described in the main manuscript. This alternative model with the PANSS subcomponents as covariates confirmed that QoL and depression fully mediated the relationship between insight and suicidality, mainly by a serial pathway, but also by a less important parallel pathway. This alternative model thus validated the mixed mediation model reported in the main manuscript.

Moreover, this model shows that positive, negative, disorganization and excitement symptoms were negatively associated with insight, but had almost no impact on suicidality and depression, except for the negative component which slightly increased the risk of depression but slightly decreased the suicidality. Finally, QoL was negatively associated with positive and negative symptoms.

MODEL INCLUDING THE CALGARY DEPRESSION SCALE (CDS) MINUS ITEM 8 (SUICIDE) AS THE MEASURE OF DEPRESSION

The CDS included an item, which specifically focused on suicide (item n°8). This item is rated by asking the following question: "Have you felt that life wasn't worth living"? "Did you ever feel like ending it all? What did you think you might do"? "Did you actually try"?
The patient's response is coded according to the following procedure:

0. Absent

1. Mild Frequent thoughts of being better off dead, or occasional thoughts of suicide.

2. Moderate deliberately considered suicide with a plan but made no attempt.

3. Severe suicidal attempt apparently designed to end in death (i.e.: accidental discovery or inefficient means).

The inclusion of a suicide item in CDS might have led to an overestimation of the strength of the relationship between depression and suicidality in the model presented in the main manuscript. We have thus run an alternative SEM analysis with the total CDS score minus item 8 as the measure of depression. The range for CDS score minus item 8 was thus 0 to 24.

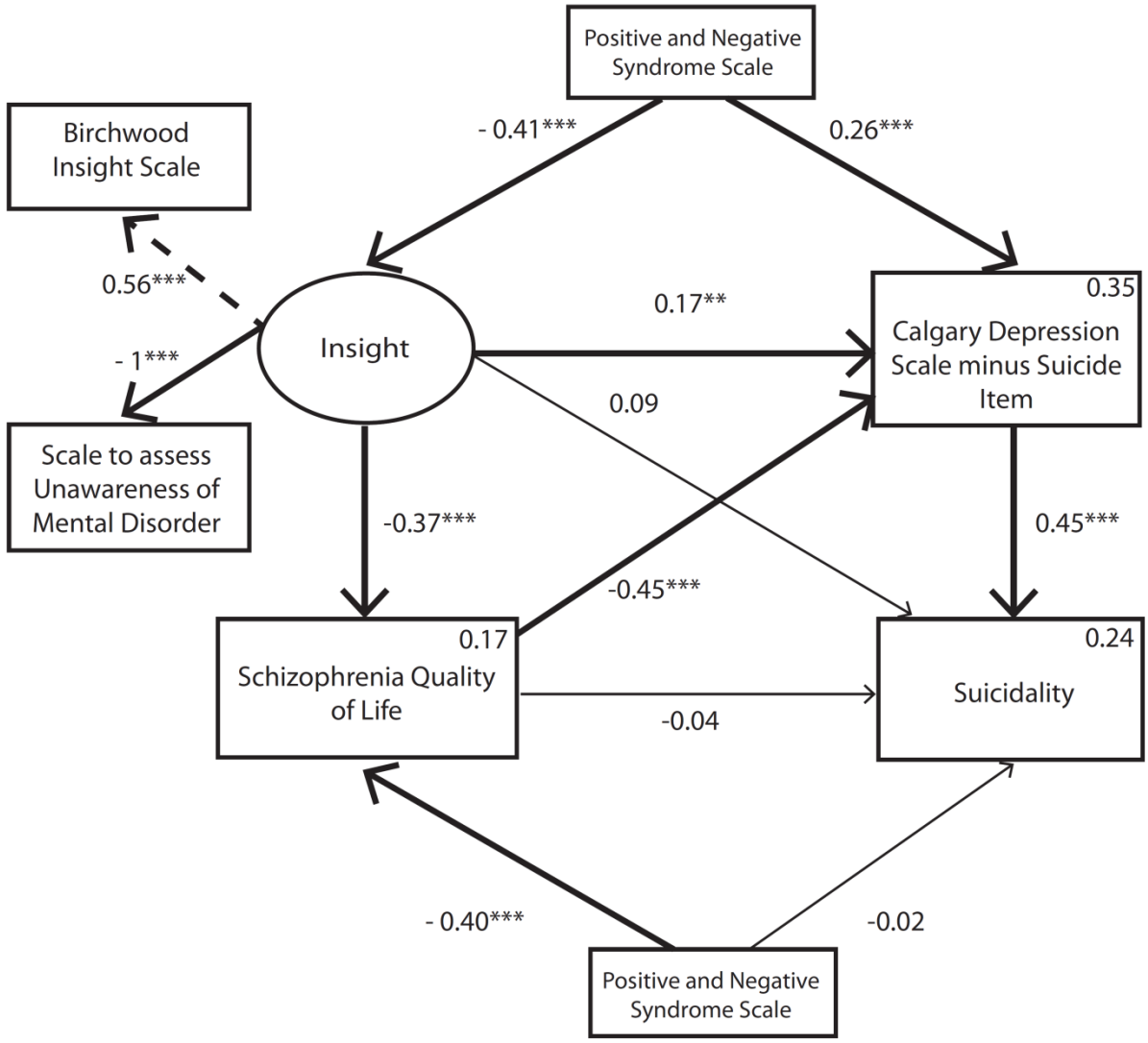
The mean CDS score minus item 8 was 3.7, SD was 4, the minimum was 0, and the maximum was 18.
Zero-order correlations between CDS score minus item 8 in one hand, and the scores on the Birchwood Insight Scale (BIS), the Scale to assess Unawareness of Mental Disorder (SUMD), the Schizophrenia Quality of Life Questionnaire (S-QoL), the suicidality and the total score on the Positive and Negative Syndrome Scale (PANSS) on the other hand were calculated with Pearson's correlation coefficients. The results are presented in the table below.

	BIS		**SUMD**		**SQoL**		**Suicidality**		**PANSS Total**	
	r	p	r	p	r	p	r	p	r	p
CDS minus item suicide	0.09	0.036	-0.18	<0.001	-0.55	<0.001	0.48	<0.001	0.30	<0.001

P-values were computed from standard errors estimated using bootstrap with 2000 iterations.

The results of the correlation analysis with CDS minus item 8 as the measure of depression were very close to the ones obtained with CDS total score (see Table 2). All the correlations between CDS minus item 8 and the other variables included in the model remained significant.

The model provided a good fit for the data, as suggested by the nonsignificant chi-square goodness-of-fit statistic ($X^2(3)=1.4$, $P=0.709$), TLI and CFI greater than 0.95 (TLI=1, CFI=1), RMSEA not significantly larger than 0.05 (RMSEA=0, 1-sided P value=0.935 for the test of the null hypothesis RMSEA=0.05), and SRMR lower than 0.08 (0.008). The model explained 23.9% of the variance in suicidality. The relationships between the variables are presented in the Figure below.



The circle represents the unobserved latent variable insight. Rectangles represent observed measured variables. Dashed arrows are drawn between a latent variable and its reference indicator with a corresponding unstandardized regression fixed to a weight of 1 (to fix the unit of measurement of each unobserved variable). Plain arrows are drawn between variables with free regression weight. The values along the plain arrow are standardized path coefficients. The squared multiple correlation (R^2) value for a dependent variable appears inside the corresponding circle or rectangle. Bold arrows are drawn between two variables that are significantly associated, whereas thin arrows are drawn between two variables that are not significantly associated. **0.01>p>0.001, ***p<0.001.

We found a significant negative association between insight and QoL; a significant negative association between insight and depression; a significant negative association between QoL and depression; and a significant positive association between depression and suicidality. The PANSS total score was negatively associated with insight and QoL. Moreover, the total PANSS score was negatively related to insight and QoL and positively linked to depression. The statistics for the estimated factor loadings and standardized path coefficients are reported in the table below.

	Variables	Estimate	Standard Error[a]	z	p
Factor loading	Insight => Birchwood Insight Scale	0.56	0.05	11.4	<0.001
	Insight => Scale to assess Unawareness of Mental Disorder	-1	0.07	-14.8	<0.001
Standardized path coefficients	Insight => Schizophrenia Quality of Life	-0.37	0.05	-6.9	<0.001
	Insight => Calgary Depression Scale minus Suicide Item	0.17	0.05	3.3	0.001
	Schizophrenia Quality of Life => Calgary Depression Scale minus Suicide Item	-0.45	0.04	-12.1	<0.001
	Insight => Suicidality	0.09	0.06	1.6	0.115
	Schizophrenia Quality of Life => Suicidality	-0.04	0.05	-0.8	0.413
	Calgary Depression Scale minus Suicide Item => Suicidality	0.45	0.05	8.7	<0.001
	Positive and Negative Syndrome Scale => Insight	-0.41	0.05	-8.9	<0.001
	Positive and Negative Syndrome Scale total score => Schizophrenia Quality of Life	-0.40	0.05	-8.2	<0.001
	Positive and Negative Syndrome Scale => Calgary Depression Scale minus Suicide Item	0.26	0.04	5.9	<0.001
	Positive and Negative Syndrome Scale => Suicidality	-0.02	0.05	-0.4	0.681

[a]Standard errors are estimated using model-based bootstrapping with 2000 iterations.

The direct effect of insight on suicidality was not significant when QoL and depression were included in the model (standardized β=0.09, standard error: 0.06, z=1.6, *P*=0.115). We found that 61.5% of the total effect of insight on suicidality was mediated by QoL and depression (standard error: 0.16, z=3.8, *P*<0.001).

Direct, indirect, and total effects between insight, QoL, and depression were all significant. We found that 65% of the total effect of insight on depression was mediated by QoL (standard error: 0.157, z=4.1, *P*<0.001).

The direct effect of QoL on suicidality was not significant when depression was included in the model (standardized β=-0.04, standard error: 0.05, z=-0.8, *P*=0.413). We found that 82.2% of the total effect of QoL on suicidality was mediated by depression (standard error: 0.187, z=4.4, *P*<0.001).

The statistics for mediation analyses coefficients are reported in the Table below.

Effect	Quality of Life				Depression (CDS minus Suicide Item)				Suicidality			
	Standardized β (or proportion)	SE[a]	z	*P* value	Standardized β (or proportion)	SE[a]	z	*P* value	Standardized β (or proportion)	SE[a]	z	*P* value
Direct effects												
Insight	-0.366	0.053	-6.9	<0.001	0.174	0.053	3.3	0.001	0.090	0.057	1.6	0.115
Quality of Life					-0.448	0.037	-12.1	<0.001	-0.043	0.053	-0.8	0.413
Depression (CDS minus Suicide Item)									0.445	0.051	8.7	<0.001
Indirect[b] effects												
Insight					0.164	0.026	6.3	<0.001	0.166	0.031	5.4	<0.001
Quality of Life									-0.20	0.028	-7.2	<0.001
Total[c] effects												
Insight	-0.366	0.053	-6.9	<0.001	0.338	0.056	6.1	<0.001	0.256	0.06	4.3	<0.001
Quality of Life					-0.448	0.037	-12.1	<0.001	-0.243	0.05	-4.8	<0.001
Depression (CDS minus Suicide Item)									0.445	0.051	8.7	<0.001
Proportion of mediated effect												
Insight					0.486	0.091	5.3	<0.001	0.650	0.157	4.1	<0.001
Quality of Life									0.822	0.187	4.4	<0.001

[a] Standard errors were estimated using model-based bootstrapping with 2000 iterations.
[b] The indirect effect of insight on suicidality includes all possible indirect paths from insight to suicidality (the path mediated by quality of life alone, the path mediated by depression alone, and the path mediated both by depression and quality of life).
[c] The total effect of insight on suicidality also includes all possible paths from insight to suicidality.

We conclude that the results were very close to the ones obtained with the total CDS score and confirmed that QoL and depression fully mediated the relationship between insight and suicidality by serial and parallel pathways. The mixed mediation model reported in the main manuscript was thus not biased by an overestimation of the relationship between depression and suicidality, which might have been caused by the inclusion of the CDS suicide item in the evaluation of depression.

MODEL INCLUDING THE CALGARY DEPRESSION SCALE (CDS) MINUS ITEM 8 (SUICIDE) AS THE MEASURE OF DEPRESSION, AND THE SUICIDE ITEM OF CDS AS THE MEASURE OF SUICIDALITY

The reliability of the associations reported in the model described in the main manuscript might have been limited by the fact that suicidality was assessed in the last 12 months. Indeed, insight is subjected to small oscillations over time in schizophrenia[4]. It is also the case of QoL[5] and depression (which tends to decrease over time[6]). We thus have reduced the temporal distance between a potiential suicidal event and the evaluation of insight, QoL, and depression to 0, by taking the item "Suicide" of CDS as the outcome of the model presented here because the assessment for CDS targeted the previous two weeks. This method ensured that a change of suicidality could not precede a change of insight and that suicidality and insight were measured simultaneously.

We have run an alternative SEM analysis with the total CDS score minus item 8 as the measure of depression, and the suicide item of CDS as the measure of suicidality. The range for suicidality was thus 0 to 3.

The mean score for CDS suicide item was 3.7, SD was 4, the minimum was 0, and the maximum was 18.

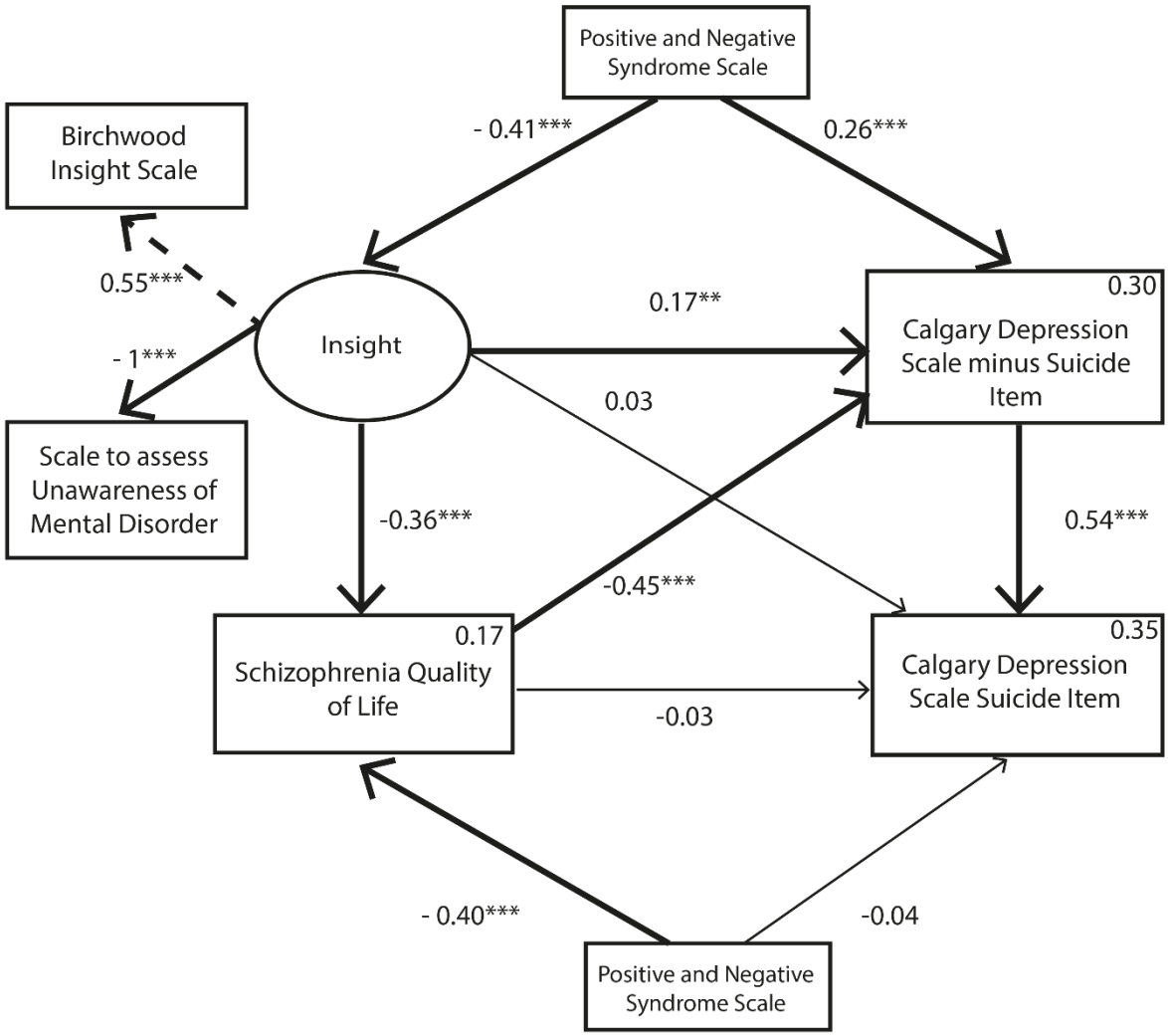
Zero-order correlations between CDS suicide item in one hand, and the scores on the Birchwood Insight Scale (BIS), the Scale to assess Unawareness of Mental Disorder (SUMD), the Schizophrenia Quality of Life Questionnaire (S-QoL), the CDS score minus suicide item, and the total score on the Positive and Negative Syndrome Scale (PANSS) on the other hand were calculated with Pearson's correlation coefficients. The results are presented in the table below.

	BIS		**SUMD**		**SQoL**		**CDS minus suicide item**		**PANSS Total**	
	r	p	r	p	r	p	r	p	r	p
CDS suicide item	0.11	0.005	-0.14	0.004	-0.32	<0.001	0.55	<0.001	0.12	0.004

P-values were computed from standard errors estimated using bootstrap with 2000 iterations.

The results of the correlation analysis with the suicide item of CDS as the measure of suicidality were very close to those obtained with the evaluation of suicidality during the last 12 months reported in the main manuscript. All the correlations between the CDS suicide item and the other variables included in the model remained significant, with the same strength.

The model provided a good fit for the data, as suggested by the nonsignificant chi-square goodness-of-fit statistic ($X^2(3)=1.3$, $P=0.719$), TLI and CFI greater than 0.95 (TLI=1, CFI=1), RMSEA not significantly larger than 0.05 (RMSEA=0, 1-sided P value=0.938 for the test of the null hypothesis RMSEA=0.05), and SRMR lower than 0.08 (0.008). The model explained 34.8% of the variance in suicidality. The relationships between the variables are presented in the Figure below.



The circle represents the unobserved latent variable insight. Rectangles represent observed measured variables. Dashed arrows are drawn between a latent variable and its reference indicator with a corresponding unstandardized regression fixed to a weight of 1 (to fix the unit of measurement of each unobserved variable). Plain arrows are drawn between variables with free regression weight. The values along the plain arrow are standardized path coefficients. The squared multiple correlation (R^2) value for a dependent variable appears inside the corresponding circle or rectangle. Bold arrows are drawn between two variables that are significantly associated, whereas thin arrows are drawn between two variables that are not significantly associated. **0.01>p>0.001, ***p<0.001.

We found a significant negative association between insight and QoL, a significant negative association between insight and depression; a significant negative association between QoL and depression; and a significant positive association between depression and suicidality. The total PANSS score was negatively related to insight and QoL and positively associated with depression. The statistics for the estimated factor loadings and standardized path coefficients are reported in the table below.

	Variables	Estimate	Standard Error[a]	z	p
Factor loading	Insight => Birchwood Insight Scale	0.55	0.05	11.3	<0.001
	Insight => Scale to assess Unawareness of Mental Disorder	-1	0.07	-14.6	<0.001
Standardized path coefficients	Insight => Schizophrenia Quality of Life	-0.36	0.05	-6.8	<0.001
	Insight => Calgary Depression Scale minus Suicide Item	0.17	0.05	3.2	0.001
	Schizophrenia Quality of Life => Calgary Depression Scale minus Suicide Item	-0.45	0.04	-12.1	<0.001
	Insight => Calgary Depression Scale Suicide Item	0.03	0.05	0.5	0.598
	Schizophrenia Quality of Life => Calgary Depression Scale Suicide Item	-0.02	0.05	-0.5	0.604
	Calgary Depression Scale minus Suicide Item => Calgary Depression Scale Suicide Item	0.54	0.05	9.9	<0.001
	Positive and Negative Syndrome Scale => Insight	-0.41	0.05	-8.8	<0.001
	Positive and Negative Syndrome Scale total score => Schizophrenia Quality of Life	-0.40	0.05	-8.1	<0.001
	Positive and Negative Syndrome Scale => Calgary Depression Scale minus Suicide Item	0.26	0.04	5.9	<0.001
	Positive and Negative Syndrome Scale => Calgary Depression Scale Suicide Item	-0.04	0.05	-0.8	0.434

[a]Standard errors are estimated using model-based bootstrapping with 2000 iterations.

The direct effect of insight on suicidality was not significant when QoL and depression were included in the model (standardized β=0.03, standard error: 0.05, z=0.5, *P*=0.598). We found that 86.7% of the total effect of insight on suicidality was mediated by QoL and depression (standard error: 0.223, z=3.9, *P*<0.001).

Direct, indirect, and total effects between insight, QoL, and depression were all significant. We found that 48.6% of the total effect of insight on depression was mediated by QoL (standard error: 0.092, z=5.3, *P*<0.001).

The direct effect of QoL on suicidality was not significant when depression was included in the model (standardized β=-0.03, standard error: 0.048, z=-0.5, *P*=0.604). We found that 90.6% of the total effect of QoL on suicidality was mediated by depression (standard error: 0.17, z=5.3, *P*<0.001).

The statistics for mediation analyses are reported in the Table below.

Effect	Quality of Life				Depression (CDS minus Suicide Item)				CDS suicide item			
	Standardized β (or proportion)	SE[a]	z	*P* value	Standardized β (or proportion)	SE[a]	z	*P* value	Standardized β (or proportion)	SE[a]	z	*P* value
Direct effects												
Insight	-0.364	0.053	-6.8	<0.001	0.172	0.053	3.2	0.001	0.029	0.054	0.5	0.598
Quality of Life					-0.448	0.037	-12.1	<0.001	-0.025	0.048	-0.5	0.604
Depression (CDS minus Suicide Item)									0.538	0.054	9.9	<0.001
Indirect[b] effects												
Insight					0.163	0.026	6.3	<0.001	0.189	0.035	5.4	<0.001
Quality of Life									-0.241	0.033	-7.4	<0.001
Total[c] effects												
Insight	-0.364	0.053	-6.8	<0.001	0.335	0.056	6	<0.001	0.218	0.057	3.9	<0.001
Quality of Life					-0.448	0.037	-12.1	<0.001	-0.266	0.043	-6.2	<0.001
Depression (CDS minus Suicide Item)									0.538	0.054	9.9	<0.001
Proportion of mediated effect												
Insight					0.486	0.092	5.3	<0.001	0.868	0.223	3.9	<0.001
Quality of Life									0.906	0.170	5.3	<0.001

[a] Standard errors were estimated using model-based bootstrapping with 2000 iterations.
[b] The indirect effect of insight on suicidality includes all possible indirect paths from insight to suicidality (the path mediated by quality of life alone, the path mediated by depression alone, and the path mediated both by depression and quality of life).
[c] The total effect of insight on suicidality also includes all possible paths from insight to suicidality.

We conclude that the results found with this evaluation of suicidality targeting the last two weeks were very close to the ones obtained with a suicidality assessment focusing on the previous 12 months. These results confirmed that QoL and depression fully mediated the relationship between insight and suicidality by serial and parallel pathways, thus validating a mixed mediation model. The mixed mediation model reported in the main manuscript was thus reliable, despite potential fluctuations of insight, depression, or QoL during the 12-month period used to assess the suicidality. The model reported in the main manuscript was thus not biased by the fact that suicide behaviors might have preceded insight variations when suicidality was evaluated in the last 12 months.

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