Association of Structural Magnetic Resonance Imaging Measures With Psychosis Onset in Individuals at Clinical High Risk for Developing Psychosis
An ENIGMA Working Group Mega-analysis

ENIGMA Clinical High Risk for Psychosis Working Group

**IMPORTANCE** The ENIGMA clinical high risk (CHR) for psychosis initiative, the largest pooled neuroimaging sample of individuals at CHR to date, aims to discover robust neurobiological markers of psychosis risk.

**OBJECTIVE** To investigate baseline structural neuroimaging differences between individuals at CHR and healthy controls as well as between participants at CHR who later developed a psychotic disorder (CHR-PS+) and those who did not (CHR-PS−).

**DESIGN, SETTING, AND PARTICIPANTS** In this case-control study, baseline T1-weighted magnetic resonance imaging (MRI) data were pooled from 31 international sites participating in the ENIGMA Clinical High Risk for Psychosis Working Group. CHR status was assessed using the Comprehensive Assessment of At-Risk Mental States or Structured Interview for Prodromal Syndromes. MRI scans were processed using harmonized protocols and analyzed within a mega-analysis and meta-analysis framework from January to October 2020.

**MAIN OUTCOMES AND MEASURES** Measures of regional cortical thickness (CT), surface area, and subcortical volumes were extracted from T1-weighted MRI scans. Independent variables were group (CHR group vs control group) and conversion status (CHR-PS+ group vs CHR-PS− group vs control group).

**RESULTS** Of the 3169 included participants, 1428 (45.1%) were female, and the mean (SD; range) age was 21.1 (4.9; 9.5-39.9) years. This study included 1792 individuals at CHR and 1377 healthy controls. Using longitudinal clinical information, 253 in the CHR-PS+ group, 1234 in the CHR-PS− group, and 305 at CHR without follow-up data were identified.

Compared with healthy controls, individuals at CHR exhibited widespread lower CT measures (mean [range] Cohen d = −0.13 [−0.17 to −0.09]), but not surface area or subcortical volume. Lower CT measures in the fusiform, superior temporal, and paracentral regions were associated with psychosis conversion (mean Cohen d = −0.22; 95% CI, −0.35 to 0.10). Among healthy controls, compared with those in the CHR-PS+ group, age showed a stronger negative association with left fusiform CT measures (F = 9.8; P < .001; q < .001) and left paracentral CT measures (F = 5.9; P = .005; q = .02). Effect sizes representing lower CT associated with psychosis conversion resembled patterns of CT differences observed in ENIGMA studies of schizophrenia (p = 0.35; 95% CI, 0.12 to 0.55; P = .004) and individuals with 22q11.2 microdeletion syndrome and a psychotic disorder diagnosis (p = 0.43; 95% CI, 0.20 to 0.61; P = .001).

**CONCLUSIONS AND RELEVANCE** This study provides evidence for widespread subtle, lower CT measures in individuals at CHR. The pattern of CT measure differences in those in the CHR-PS+ group was similar to those reported in other large-scale investigations of psychosis. Additionally, a subset of these regions displayed abnormal age associations. Widespread disruptions in CT coupled with abnormal age associations in those at CHR may point to disruptions in postnatal brain developmental processes.
The clinical high-risk (CHR) paradigm is a widely used framework to investigate mechanisms underlying psychosis vulnerability. Help-seeking individuals who do not meet diagnostic criteria for a psychotic disorder but typically present with subthreshold psychotic symptoms and accumulating risk factors are considered at CHR for developing psychosis. An estimated 18% to 20% of individuals at CHR develop a psychotic disorder within 2 years of identification, although conversion rates vary, likely due to heterogeneous recruitment and sampling strategies as well as interventions applied. However, despite decades of research, the nature of morphometrical differences associated with psychosis conversion remains largely unknown. Here, we aim to address this question by combining all available structural neuroimaging data in CHR to date in an attempt to better understand group differences associated with psychosis risk and conversion in this population.

A large body of work has used structural magnetic resonance imaging (sMRI) to investigate morphometric brain differences in individuals at CHR. However, the extent to which characteristic baseline (ie, when participants are initially ascertained and assessed at a first study visit) structural neuroimaging differences exist between those at CHR who later develop a psychotic disorder (CHR-PS+) compared with those who do not (CHR-PS−) is debated. Many studies failed to find baseline differences between these 2 groups, although a meta-analysis and multicenter study found lower prefrontal and temporal volumes or cortical thickness measured by MRI (which we will refer to as CT) in individuals at CHR who developed a psychotic disorder. High attrition rates in samples of individuals at CHR coupled with low psychosis conversion rates often yielded insufficient power to detect between-group structural brain differences. Moreover, small sample sizes can be associated with inflated effect sizes, so effect sizes of prior studies that found structural brain differences in individuals at CHR may be overestimated. Although multisite consortia aim to address these challenges, to our knowledge, the largest published sMRI studies to date included fewer than 50 individuals at CHR who later developed a psychotic disorder. Furthermore, it is currently unknown whether group differences are robust enough to predict outcomes.

Importantly, many participants at CHR are adolescents or young adults, a timeframe associated with psychosis onset. Prefrontal-temporal brain regions, which are typically implicated in psychosis, show protracted developmental courses continuing through adolescence, suggesting that morphometric differences associated with psychosis risk vary with age. Indeed, there are developmental influences on psychotic symptom presentation, perhaps driven by differences in regional brain changes. It is not fully understood how age-related patterns in brain morphometry in individuals at CHR differ from normal development. Thus, using a developmental framework to examine whether morphometric differences in individuals at CHR are influenced by age may provide important insights into mechanisms associated with psychosis risk and the stability of neuroimaging measures associated with psychosis risk across development.

Finally, to our knowledge, it is unknown whether baseline brain differences associated with future conversion to psychosis resemble those observed in other large-scale psychosis studies. Understanding whether morphometric differences in individuals at CHR overlap with those observed in individuals who have schizophrenia and individuals with a genetic subtype of psychosis will provide insights into convergent or distinct differences across the psychosis spectrum.

To address these questions, we founded the Enhancing Neuro Imaging Genetics Through Meta-Analysis (ENIGMA) Clinical High Risk for Psychosis Working Group in 2018. Using baseline sMRI data and longitudinal clinical information from 31 sites, this study addressed the following questions:

1. Do participants at CHR and healthy controls differ in CT, surface area (SA), and/or subcortical volumes?
2. Is there a neuroanatomic signature associated with future transition to a psychotic disorder (CHR-PS+ group vs CHR-PS− group vs control group)?
3. Do structural neuroimaging measures identified in aims 1 and 2 display group differences in age associations suggestive of abnormal developmental trajectories?
4. Is the pattern of morphometric alteration associated with psychosis conversion similar to that observed in other ENIGMA studies of psychosis?

Methods
Participants
We included 1792 individuals at CHR, including 253 in the CHR-PS+ group, 1234 in the CHR-PS− group, and 305 without follow-up data, and 1377 healthy controls from 31 sites participating in the ENIGMA Clinical High Risk for Psychosis Working Group (Table). Participants met the Comprehensive Assessment of At-Risk Mental States (CAARMS; n = 821) or Structured Interview for Prodromal Syndromes (SIPS; n = 971) CHR criteria (Methods in the Supplement). Site-specific inclusion and exclusion criteria are detailed in eTable 1 in the Supplement. All sites obtained local institutional review board approval prior to data collection. Informed written consent was
obtained from every participant or the participant’s guardian for participants younger than 18 years. All studies were conducted in accordance with the Declaration of Helsinki.36

**Image Acquisition and Processing**

A total of 31 sites contributed T1-weighted MRI brain scans from 50 MRI scanners, including 42 3-T scanners and 8 1.5-T scanners (eTable 2 in the Supplement). Scanners were manufactured by Siemens (n = 23), Philips (n = 8), GE (n = 18), and Toshiba (n = 1). A breakdown of the number of scans obtained for those in the CHR-PS+, CHR-PS−, and control groups for each scanner is reported in eTable 3 in the Supplement. After processing the data using FreeSurfer analysis software (eTable 2 in the Supplement),37-39 we extracted 68 CT, 68 SA, and 16 subcortical volume measures. We also examined 3 global neuroimaging measures—total intracranial volume (ICV), mean CT, and total SA—resulting in 155 neuroimaging measures. We implemented the ENIGMA consortium quality assessment pipeline.32-35,40,41 A priori power calculations are included in eMethods in the Supplement.

**Statistical Analyses**

**Group-Related and Conversion-Related Differences in sMRI Metrics**

We assessed group differences using general linear models (GLMs) within a mega-analysis framework, with each sMRI measure (ie, CT, SA, or subcortical volume) as the dependent variable and group (CHR or healthy control) or conversion status (CHR-PS+, CHR-PS−, or control) as the independent variable. We included age, age², sex, and estimated total ICV as covariates in all models and corrected for multiple comparisons (n = 155) using the false discovery rate method.42 q Values less than .05 were considered statistically significant. Significance for P values for minimal-effects testing was set at P < .05 and were 1-tailed; all other P and q values were 2-tailed. All analyses were conducted using R version 3.6.3 (The R Foundation).

For all structural neuroimaging measures, we calculated Cohen d effect sizes from the GLMs between 2 (individuals at CHR vs healthy controls) or 3 groups of interest (CHR-PS+ group vs control group; CHR-PS+ group vs CHR-PS− group; CHR-PS− group vs control group). Based on recent work demonstrating that neuroComBat harmonization increases statistical power within a mega-analytic framework,43 primary analyses were conducted within a mega-analysis framework using data that were co-

---

Table. Age and Sex Information for Healthy Controls and Participants at Clinical High Risk (CHR) for Psychosis at Each Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Control group Individuals at CHR</th>
<th>CHR-PS+ group a</th>
<th>CHR-PS− group a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam</td>
<td>33</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Barcelona-HSJD</td>
<td>54</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Columbia1</td>
<td>55</td>
<td>32</td>
<td>23</td>
</tr>
<tr>
<td>Columbia2</td>
<td>58</td>
<td>35</td>
<td>23</td>
</tr>
<tr>
<td>Columbia3</td>
<td>17</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Florence</td>
<td>22</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Genova</td>
<td>32</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Heidelberg</td>
<td>33</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>IDIBAPS</td>
<td>38</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Melbourne</td>
<td>92</td>
<td>42</td>
<td>24</td>
</tr>
<tr>
<td>New York</td>
<td>50</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Nashville</td>
<td>50</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Toronto</td>
<td>50</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Tokyo</td>
<td>10</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

(continued)
Table. Age and Sex Information for Healthy Controls and Participants at Clinical High Risk (CHR) for Psychosis at Each Site (continued)

<table>
<thead>
<tr>
<th>Site</th>
<th>No. (%</th>
<th>Age, mean (SD; range), y</th>
<th>Transition length, mean (SD), mo</th>
<th>Follow-up length, mean (SD), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam</td>
<td>79</td>
<td>23 (1.9; 2-18.9)</td>
<td>0.7 (1.1)</td>
<td>6.8 (1.2)</td>
</tr>
<tr>
<td>Barcelona</td>
<td>84</td>
<td>22 (1.6; 2-18.4)</td>
<td>1.1 (1.5)</td>
<td>6.9 (1.5)</td>
</tr>
<tr>
<td>Bern</td>
<td>21</td>
<td>19 (0.9; 18-21)</td>
<td>0.5 (1.1)</td>
<td>6.5 (1.3)</td>
</tr>
<tr>
<td>Columbia</td>
<td>102</td>
<td>21 (1.5; 18-25)</td>
<td>0.7 (1.2)</td>
<td>6.8 (1.2)</td>
</tr>
<tr>
<td>Copenhagen</td>
<td>102</td>
<td>21 (1.2; 18-25)</td>
<td>0.7 (1.2)</td>
<td>6.8 (1.2)</td>
</tr>
<tr>
<td>CSU</td>
<td>79</td>
<td>23 (1.9; 2-18.9)</td>
<td>0.7 (1.1)</td>
<td>6.8 (1.2)</td>
</tr>
<tr>
<td>Glasgow</td>
<td>74</td>
<td>21 (1.7; 18-25)</td>
<td>0.7 (1.2)</td>
<td>6.8 (1.2)</td>
</tr>
<tr>
<td>Heidelberg</td>
<td>16</td>
<td>12 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>IDIBAPS</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Icahn</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>King's College</td>
<td>74</td>
<td>21 (1.7; 18-25)</td>
<td>0.7 (1.2)</td>
<td>6.8 (1.2)</td>
</tr>
<tr>
<td>Maastricht</td>
<td>84</td>
<td>22 (1.6; 2-18.4)</td>
<td>1.1 (1.5)</td>
<td>6.9 (1.5)</td>
</tr>
<tr>
<td>Melbourne</td>
<td>24</td>
<td>11 (0.5; 11-18)</td>
<td>0.5 (1.1)</td>
<td>6.5 (1.3)</td>
</tr>
<tr>
<td>Mexico City</td>
<td>102</td>
<td>21 (1.2; 18-25)</td>
<td>0.7 (1.2)</td>
<td>6.8 (1.2)</td>
</tr>
<tr>
<td>Moscow</td>
<td>24</td>
<td>11 (0.5; 11-18)</td>
<td>0.5 (1.1)</td>
<td>6.5 (1.3)</td>
</tr>
<tr>
<td>MPRC</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>New York</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Newcastle</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Oslo</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Rush</td>
<td>102</td>
<td>21 (1.5; 18-25)</td>
<td>0.7 (1.2)</td>
<td>6.8 (1.2)</td>
</tr>
<tr>
<td>Singapore</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Stavanger</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Sydney</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Stavanger</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Sydney</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Toho</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Toronto</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
<tr>
<td>Toyama</td>
<td>25</td>
<td>13 (0.6; 12-18)</td>
<td>0.6 (1.1)</td>
<td>6.6 (1.1)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; CHR-PS+, individuals at CHR who later developed a psychotic disorder; CHR-PS−, individuals at CHR who did not later develop a psychotic disorder.

Values for the CHR-PS+ and CHR-PS− groupsdonot alwayssumto thenumber ofindividualsat CHResteachsitebecause therewereindividualsat CHRwithout follow-updata (n = 305).

Data were not available either becausenoindividualsat CHRtransitioneda psychotichdisorder orbecause follow-updatawere not available.

Additional sitedetailscanbefoundineTable 1 in the Supplement.

To evaluate the stability of group and conversion status differences, we performed analyses statistically controlling for baseline psychotropic medication exposure. Toassessiteffects, we conductedjackknife resampling analyses, ie, iteratively removing one site’s data and rerunning respective analyses.44 sMRI measures that failed to show a group or conversion status association at a q value less than 0.05 in more than 10% jackknife iterations (ie, 4 of 31 sites) were considered unstable.

To assess the meaningfulness of obtained effect sizes, we used 2 analytic approaches: equivalence testing (to assess whether observed differences fell within the upper and lower bounds of a predefined smallest effect size of interest, providing support for the absence of a meaningful effect) and minimal-effects testing (to assess whether observed effects were greater than the same predefined effect size).45 Upper and lower bounds (representing the positive and negative predefined smallest effect size of interest) were set to a Cohen d of 0.15 and −0.15, respectively (eMethods in the Supplement).

Group and Conversion-Related Differences in sMRI Age Associations

We used general additive models (GAMs)46,47 to model group and conversion status differences in the association between age and sMRI measures (eMethods in the Supplement). First, we examined the interaction between group (individuals at CHR vs healthy controls) and age in the 56 neuroimaging measures that differed at a q value less than 0.05 between healthy controls and individuals at CHR. Next, we conducted GAM analyses on the 4 sMRI measures on which the CHR-PS+, CHR-PS−, and control groups differed from each other (ie, left paracentral CT, right paracentral CT, left fusiform CT, right superior temporal CT) in analy-
ses of psychosis conversion. We examined the associations of baseline age and group/conversion status as well as the interaction between the 2 variables. Sex and estimated ICV were included as covariates. Similar to previous work examining age associations during adolescent development, we restricted our sample's age range to 12 to 25 years (eTable 4 in the Supplement). Details on post hoc analyses for significant interaction associations are provided in the eMethods in the Supplement.

Comparison of Psychosis Conversion Effect Sizes With Findings of Other ENIGMA Studies

We computed Spearman rank correlations to assess the extent to which the pattern of observed effect sizes (Cohen d for CHR-PS+ and CHR-PS− groups vs control group) correlated with the pattern found in prior psychosis studies, specifically the ENIGMA Schizophrenia Working Group (individuals with schizophrenia vs healthy controls) and ENIGMA 22q11.2 Deletion Syndrome Working Group (individuals with 22q11.2 deletion syndrome with psychosis vs those with 22q11.2 deletion syndrome without psychosis). As a control, we compared the effect sizes of the CHR-PS+ group and CHR-PS− group vs control group with the effect sizes of the major depressive disorder (MDD) group vs control group published by the ENIGMA Major Depressive Disorder Working Group (eMethods in the Supplement).

Results

Sample Characteristics

Of the 3169 included participants, 1428 (45.1%) were female, and the mean (SD; range) age was 21.1 (4.9; 9.5–39.9) years (Table). Intelligence quotient (IQ) comparisons between healthy controls and individuals at CHR are reported in eTable 5 in the Supplement. Within each site, baseline IQ measures were largely similar in all participants at CHR, including those in the CHR-PS+ group, CHR-PS− group, and participants at CHR without follow-up information (eTable 6 in the Supplement). For symptom measures, participants at CHR without follow-up data had less severe baseline positive, negative, and disorganized symptoms on the SIPS compared with participants in the CHR-PS+ and CHR-PS− groups (eTable 7 in the Supplement). Compared with the CHR-PS+ and CHR-PS− groups, those without follow-up data had less severe cognitive changes on the CAARMS (eTable 7 in the Supplement). Few participants at CHR reported typical (less than 1%) and/or atypical (12.4%) antipsychotic medication use (eTable 8 in the Supplement).

CT in Participants at CHR vs Healthy Controls

In neuroComBat-harmonized GLM mega-analyses, participants at CHR had smaller global neuroimaging measures compared with healthy controls (estimated ICV: Cohen d = −0.13; 95% CI, −0.20 to −0.06; mean CT: Cohen d = −0.18; 95% CI, −0.25 to −0.11; total SA: Cohen d = −0.15; 95% CI, −0.22 to −0.08). We also observed significant group associations in 53 additional GLMs (eTable 9 in the Supplement). The largest group associations were observed for widespread lower CT in individuals at CHR vs healthy controls (42 of 68 comparisons; Cohen d range, −0.17 to −0.09) (Figure 1A; eTable 9 and eFigure 1 in the Supplement). Few subcortical (3 of 16) and SA (8 of 68) group differences were observed. No group × sex interactions were detected.

We present results of possible confound analyses, including ICV, medication and site associations, equivalence testing, and results of neuroComBat harmonization in eTables 10 to 13 and eFigures 1 and 2 in the Supplement. No sMRI measures were uniquely sensitive to psychosis-risk syndrome (eResults and eTables 14 to 17 in the Supplement).

Association of Paracentral, Fusiform, and Superior Temporal CT With Psychosis Conversion

A total of 48 structural neuroimaging measures exhibited a significant overall association with psychosis conversion status in GLM mega-analyses using neuroComBat harmonized data (Figure 1B; eTable 18 and eFigure 3 in the Supplement). Most significant differences were observed for CT measures (n = 37). Within these 48 regions, we conducted pairwise GLMs between the CHR-PS+ and control groups, CHR-PS− and control groups, and CHR-PS+ and CHR-PS− groups. Of these 48 regions, the CHR-PS+ group differed from the CHR-PS− and control groups on 4 neuroimaging measures.

Compared with the control and CHR-PS− groups, the CHR-PS+ group exhibited lower CT in bilateral paracentral, right superior temporal, and left fusiform regions (mean Cohen d of 4 sMRI measures = −0.22; 95% CI, −0.35 to 0.10). Similar findings were observed for the left superior temporal and right fusiform regions. Moreover, the CHR-PS+ and CHR-PS− groups exhibited thinner cortex in bilateral paracentral, superior temporal, and fusiform regions compared with the control group (Figure 2). Using minimal-effects testing, we observed that effect sizes for bilateral paracentral (left hemisphere: z = −2.43; P = .02; right hemisphere: z = −1.86; P = .06), right superior temporal (z = −2.29; P = .02), and left fusiform (z = −2.00; P = .05) in the CHR-PS+ group vs the control group were all greater than 0.15, except for the right paracentral region, underscoring the presence of notable group differences.

In all remaining comparisons of regions that exhibited a statistically significant association with psychosis conversion status, the CHR-PS+ and CHR-PS− groups significantly differed from the control group at P < .05. However, the CHR-PS+ group did not differ from the CHR-PS− group in any remaining comparisons (eTable 18 in the Supplement). We observed no conversion status × sex interactions, and results remained stable when length of follow-up period was included as a covariate.

We present results of confound analyses (medication, site associations, equivalence testing) in the eResults, eTables 19 to 21, and eFigure 2 in the Supplement. There were no statistically significant psychosis risk syndrome × conversion status interactions (eResults and eTable 22 in the Supplement).

Age Associations in CHR-PS+ and CHR-PS− Groups Compared With Control Group

In GAM analyses, we observed no statistically significant group × age interactions for the 56 neuroimaging measures that differed
between individuals at CHR and healthy controls (eTable 23 in the Supplement). We then conducted GAM analyses on the 4 sMRI measures on which the CHR-PS+ group displayed lower CT compared with the CHR-PS− and control groups in psychosis conversion group analyses. These sMRI measures were left paracentral CT, right paracentral CT, left fusiform CT, and right superior temporal CT. Two measures displayed a significant psychosis conversion status × age interaction. For each group × age interaction analysis, we assessed group differences in age associations (ie, CHR-PS+ group vs control group, CHR-PS− group vs control group, and CHR-PS+ group vs CHR-PS− group).

In left fusiform, the association of age with CT differed between the CHR-PS+ group and control group ($F = 5.9; P < .005$; $q < .02$) (Figure 2A) but not between the CHR-PS+ group and control group ($F = 0.2; P = .68; q = .74$) or the CHR-PS+ group and CHR-PS− group ($F = 1.9; P = .18; q = .45$). Among individuals aged 12 to 15.8 years, those in the control group showed a stronger negative association of age with CT compared with those in the CHR-PS+ and CHR-PS− groups. Although the interaction was not statistically significant, a similar pattern emerged for the right fusiform CT (Figure 3A; eTable 24 in the Supplement).

Age associations in the left paracentral CT differed between the CHR-PS+ group and control group ($F = 5.9; P < .005; q < .02$) (Figure 2B) but not between the CHR-PS− group and control group ($F = 0.2; P = .68; q = .74$) or the CHR-PS+ group and CHR-PS− group ($F = 1.9; P = .18; q = .45$). Among individuals aged 12 to 15.8 years, those in the control group showed a stronger negative association of age with CT compared with those in the CHR-PS+ group. The association of age with CT did not differ between the CHR-PS− group and control group ($F = 0.2; P = .68; q = .74$). This pattern of results was not observed for the right paracentral CT (Figure 3B; eTable 24 in the Supplement). We found no significant age × conver-
sion status interactions for the superior temporal CT (Figure 3C; eTable 24 in the Supplement); all groups showed negative associations of age with CT.

CT in the ENIGMA CHR Group Compared With Other ENIGMA Working Groups

eFigure 4 in the Supplement provides a visual overview of CT differences in the CHR-PS+ group, individuals with schizophrenia (using published data from the ENIGMA Schizophrenia Working Group32,33), and individuals with 22q11.2 deletion syndrome and a psychotic disorder (using published data from the ENIGMA 22q11.2 Deletion Syndrome Working Group34,35).

The overall pattern of baseline CT differences in the CHR-PS+ group relative to the control group was significantly correlated with that observed in individuals with schizophrenia (ρ = 0.35; 95% CI, 0.12 to 0.55; P = .004) and in individuals with 22q11.2 deletion syndrome and a psychotic disorder (using published data from the ENIGMA 22q11.2 Deletion Syndrome Working Group34,35).

Supplement). Associations involving CHR-PS− vs control CT, SA, and subcortical volume differences were similar to those reported here (eResults in the Supplement).

Discussion

We conducted, to our knowledge, the largest multisite neuroimaging investigation to date in participants at CHR, examining baseline structural neuroimaging measures associated with later transition to psychosis. We found widespread lower CT in individuals at CHR, consistent with previously reported CT differences in individuals with an established psychotic disorder. Compared with those in the CHR-PS+ and control groups, at baseline, those in the CHR-PS+ group exhibited thinner cortex in bilateral paracentral, right fusiform, and left superior temporal regions, with effect sizes significantly greater than what we considered to be meaningful a priori. Our results were robust to associations of medication exposure, sex, site, and length of follow-up period. Findings from this international effort suggest that conversion to psychosis among those at CHR is associated with lower CT at baseline.

We identified widespread regional lower CT in individuals at CHR compared with healthy controls. Lower CT has been observed in individuals with schizophrenia as well as other psychiatric disorders.32,40,50 Importantly, the overall pattern of lower CT in those in the CHR-PS+ and CHR-PS− groups resembled that observed in individuals with schizophrenia and individuals with 22q11.2 deletion syndrome and a psychotic disorder but not in individuals with MDD. For the CHR-PS+ group, correlations with CT differences in individuals with schizophrenia were significantly greater than the association observed with CT differences in individuals with MDD. Taken together, our results suggest that the overall constellation of reported CT differences in individuals at CHR resembles the
Figure 3. Age Associations of Regions That Exhibited an Association of Conversion Status

A. Age vs fusiform cortical thickness

B. Age vs paracentral thickness

C. Age vs superior temporal thickness

Each graph has a line of best fit for the association of age with the respective neuroimaging measures. Shading around the line indicates the SE. The bars underneath the age plots reflect the derivative of the slope, i.e., the rate of change taking place at a particular age, scaled as a pseudo t statistic, based on the posterior simulation. CHR-PS+ indicates individuals at clinical high risk who later developed a psychotic disorder; CHR-PS−, individuals at clinical high risk who did not later develop a psychotic disorder.
general pattern of CT differences observed in individuals with schizophrenia and genetic disorders associated with psychosis and thus suggest that widespread thinner cortex in individuals at CHR may be associated with their increased risk of psychosis.

We also found that lower CT in paracentral, superior temporal, and fusiform regions was associated with psychosis conversion; individuals in the CHR-PS+ group exhibited significantly lower CT than those in the CHR-PS− group and control group in these regions. Lower baseline CT and/or volume in these regions has previously been reported in individuals at CHR who later developed a psychotic disorder (data not used here). Furthermore, longitudinal CT decreases in these regions have been associated with transition to psychosis in those at CHR. The magnitude of altered CT in individuals in the CHR-PS+ group in the paracentral, superior temporal, and fusiform regions was highly consistent with findings in individuals with schizophrenia, and lower fusiform and paracentral CT has been observed in individuals in who hear voices but do not have a diagnosis of schizophrenia. Given that both help-seeking and non-help-seeking individuals on the psychosis spectrum exhibit alterations in these regions, CT in the paracentral, superior temporal, and fusiform areas may display a dose-response association with psychosis risk. While this interpretation also aligns with our observation that CT in these regions differed between the CHR-PS+, CHR-PS−, and control group (with the lowest CT for those in the CHR-PS+ group), this explanation remains speculative in light of the cross-sectional nature of the data.

Consistent with previous CHR studies examining baseline neuroimaging associations with later conversion to psychosis, we did not observe widespread subcortical volume or SA differences associated with later psychosis transition. Taken together, these results suggest that CT reductions may be among the most widespread, robust, and specific morphometric changes associated with psychosis risk and conversion compared with SA or subcortical volume.

An intriguing pattern of findings emerged from the psychosis conversion + age analyses. Compared with the control group, the CHR-PS+ and CHR-PS− groups exhibited significantly lower paracentral and fusiform region CT among those aged 12 to 16 years. Our analyses investigating age-associated rates of change (estimated using cross-sectional data) seemed to indicate a steeper decline in slope for those in the control group during this time frame, which reached a plateau in adulthood. However, those in the CHR-PS− group displayed a slower decline, and results in the CHR-PS+ group were indicative of a reduced or delayed rate of change. Relative to the normative timetable in healthy controls, these findings may suggest an accelerated developmental decrease in paracentral and/or fusiform CT in the CHR-PS+ and CHR-PS− groups, with the greatest declines occurring in the CHR-PS+ group. If indeed normative CT decreases during adolescence represent a period of specialization (where higher-level systems that contribute to adult outcomes are formed), lower CT, most apparent in those in the CHR-PS+ group, could reflect impairments in optimal specialization. However, these observations are speculative, and the veracity of these patterns will be most accurately captured with longitudinal analyses that encompass a wide age range (eg, early childhood through adulthood).

The neuroanatomic pattern of group differences and age-associated disruptions observed in individuals at CHR may provide important insights into mechanisms underlying increased risk of psychosis. Preclinical models and recent genome-wide association studies suggest that genetic variants associated with SA are linked to the regulation of neural progenitor cells during fetal development, while genetic markers associated with CT are associated with regulatory processes in adulthood. Thus, CT differences may be the end result of maladaptive maturation-related mechanisms that occur during postfetal development, including proliferation, synaptic pruning, and/or myelination. Thinner CT, particularly in early adolescence (Figure 3), could reflect abnormal synaptic plasticity or pruning, which have both been implicated in in vitro schizophrenia models. Although excessive synaptic pruning is one plausible explanation for thinner cortex associated with psychosis transition, recent evidence suggests that intracortical myelination and/or expression of myelin-related genes may be mechanisms of cortical thinning.

To better understand neurobiological mechanisms underlying psychosis transition in individuals at CHR, investigations of concomitant measures of CT, macroscale white matter tracts, and intracortical myelination are necessary. Finally, it is also possible that lower CT is not a mechanism of psychosis and can instead be attributed to environmental factors or social determinants associated with psychosis, or that lower CT occurs in response to other possible biological mechanisms underlying psychosis (eg, hypothalamic-pituitary-adrenal stress response).

Even if CT reductions in individuals at CHR were robust, effect sizes for between-group differences were nevertheless small to moderate and accounted for approximately 1% of the variance in comparisons between the CHR-PS+ and CHR-PS− groups. The subtle nature of these morphometric differences underscores the importance of adequate statistical power, achievable only through large-scale multisite collaborations. Consistent with recent work showing that schizophrenia polygenic risk scores only improved differentiation of individuals in the CHR-PS+ group from controls (and not those in the CHR-PS+ group from those in the CHR-PS− group), we anticipate that baseline, univariate sMRI metrics will have a similar impact on psychosis risk prediction algorithms. Given the logistic and financial challenges that MRI brings, the use of MRI metrics in isolation may not be feasible or useful for psychosis risk prediction. A viable solution may be to adopt sequential assessment frameworks, as recently implemented. Alternatively, sMRI differences may be a better predictor of general psychopathology and would be better suited for transdiagnostic risk prediction models.

Limitations
Our study had limitations. One limitation common to multisite studies is that data were collected from multiple scan-
nners, although leave-1-out analyses suggest that site associations were not prominent. Second, this initial study focused on baseline cross-sectional data and did not investigate progressive sMRI changes associated with psychosis conversion, as identified in prior work.6,18–21,72 Additionally, CHR status is associated with heterogeneous outcomes,73–75 and neuro-imaging phenotypes may differentiate among variability in psychosocial functioning and/or among other psychiatric diagnoses (eg, mood and anxiety disorders). These are two future goals of the ENIGMA Clinical High Risk for Psychosis Working Group, now that feasibility of this collaboration has been established.

Conclusions

In the largest study of brain abnormalities in individuals at CHR to date, we found robust evidence of a subtle, widespread pattern of CT differences, consistent with observations in psychosis. The specificity of these differences to CT—as well as age-associated deviations in regions sensitive to psychosis conversion—may point to abnormal development processes. These findings also point to age ranges (ie, early adolescence) when morphometric abnormalities in individuals at CHR might be greatest.

ARTICLE INFORMATION

Accepted for Publication: March 4, 2021.
Published Online: May 5, 2021.

ENIGMA Clinical High Risk for Psychosis Working Group Authors: Maria Jalbrzikowski, PhD; Rebecca A. Hayes, PhD; Stephen J. Wood, PhD; Dorte Nordholm, MD, PhD; Juan H. Zhou, PhD; Paolo Fusar-Poli, MD, PhD; Peter J. Uhlhaas, PhD; Tsutomu Takahashi, MD, PhD; Gisela Sugranyes, MD; Yoosun Yoon, BA; Daniel H. Mathalon, MD, PhD; Naoyuki Katagiri, MD, PhD; Christine I. Hooker, Lukasz Smigielski, PhD; Tiziano Colizatti, MD; Esther Via, MD, PhD; Jinsong Tang, PhD; Shinusuke Koike, MD, PhD; Paul E. Rasser, MSc; Chantal Michel, PhD; Irina Lebedeva, PhD; DSCi; Wenche ten Velden Hegelstad, PhD; Camilo de la Fuente-Sandoval, MD, PhD; James A. Waltz, PhD; Romina Mizrahi, MD, PhD; Cheryl M. Corcoran, MD; Franz Resch, MD; Christian K. Tannnes, PhD; Shalala S. Haas, PhD; Inkke L. Lemmers-Jansen, MD, PhD; Ingrid Agartz, MD, PhD; Paul Allen, PhD; G. Paul Amminger, MD, PhD; Ole A. Andreassen, PhD; Kimberly Atkinson, MSc; Peter Bachman, PhD; Inmaculada Baeza, MD, PhD; Helen Baldwin, MSc; Cali F. Bartholomeusz, PhD; Stefan Borgwardt, MD; Sabrina Catalano; Michael W. L. Chee, MBBS; Xiaogang Chen, MD, PhD; Kang S K. Cho, PhD; Rebecca E. Cooper, BBmed(hons); Vanessa L. Crockley, PhD; Montserrat Dölz, MD; Bjorn H. Ebdrup, MD, PhD; Adriana Forteza, MD; Louise Birkedal Genthag, MSc, PhD; Birte Y. Ghentag, MDDrMedSci; Lieuwe de Haan, MD, PhD; Holly K. Hamilton, PhD; Mathew A. Harris, PhD; Kristen M. Hau, PhD; Ying He, MD, PhD; Karsten Heereken, MD; MA, Andreas Heinz, MD, PhD; Daniela Hubl, MD; Wu Jeong Hwang, BBmed(hons); Michael Kaes, MD; Kiyoto Katsai, MD; Minh Nin, MD, PhD; Jochen Kindler, MD; Mallory J. Laukin, PhD; Alex Koppel, HBSc; Tina D. Kristensen, PhD; Jun Soo Kwon, MD, PhD; Stephen M. Lawrie, MD, PhD; Jimmy Lee, MBBS, MMed, Pablo León-Ortiz, MD, PhD; Ashleigh Lin, PhD; Rachel L. Loewy, PhD; Xiaojian Ma, MD, Patricia McCrory, MD, PhD, Philip McGuire, MD, PhD; Masafumi Mizuno, MD, PhD; Paul Meller, MD; Tomas Moncada-Habib, MD; Daniel Muñoz-Samons, MD; Barnaby Nelson, PhD, Takahiro Nemoto, MD, PhD; Michele Rasser, MD, DrMedSci; Maria A. Omelechenko, PhD; Ketil Oppedal, MD; Lijun Ouyang, MD; Christos Pantelis, MD; Jose C. Pariente, MSc; Jayachandra M. Raghava, PhD; Francisco Reyes-Madrigal, MD, MSc; Brian J. Roach, MD, Ian J. Rassberg, MD, PhD; Wulf Rösler, MD, MSc; Dean F. Salisbury, MD, PhD; Daisi Sasabasyahi, MD, PhD; Ulrich Schall, MD, PhD, DSc; Jason Schiffman, PhD; Florian Schlagenhauf, MD, PhD; Andre Schmidt, PhD; Mikkel E. Sørensen, MSc; Michio Suzuki, MD, PhD; Anastasia Theodoridou, MD, PhD; Alexander S. Tomyszew, MSc; Jordina Tor, MSc; Tor G. Vennes, MD; Velakoulis, MD; Gloria D. Venegoni, MSc; Sophia Vinogradov, MD; Christina Wenneberg, MD, PhD; Lars T. Westlye, MD; Hidenori Yamase, MD, PhD; Liu Yuan, MD; Alison R. Yung, MD, PhD; Thérèse A. M. J. van Amelsvoort, MD, PhD; Jessica A. Turner, PhD; Theo G. M. van Erp, PhD; Paul M. Thompson, PhD; Dennis Hernaus, PhD.

Affiliations of ENIGMA Clinical High Risk for Psychosis Working Group Authors: Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania (Jalbrzikowski, Hayes, Bachman, Catalano, Salisu); Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia (Wood, Amminger, Bartholomeusz, McGorry, Nelson, Yung); Dágina, Melbourne, Australia (Wood, Amminger, Bartholomeusz, McGorry, Nelson, Yung); School of Psychology, University of Birmingham, Birmingham, United Kingdom (Wood); Copenhagen Research Center for Mental Health, Mental Health Center Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark (Nordholm, L. B. Ghentag, Kristensen, Nordentoft, Wenneberg); Center for Sleep and Cognition, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (Zhou, Chee); Center for Translational Magnetic Resonance Research, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (Zhou); Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy (Fusar-Poli); EPIC Lab, Department of Psychology Studies, King's College London, London, United Kingdom (Fusar-Poli); Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany (Uhlhaas); Institute of Neuroscience and Psychology, University of Glasgow, United Kingdom (Uhlhaas); Department of Neuropsychiatry, University of Toyoama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan (Takahashi, Sasabasyahi, Suzuki); Research Center for Idling Brain Science, University of Toyoama, Toyama, Japan (Takahashi, Sasabasyahi, Suzuki); Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany (Uhlhaas); Instituto de Neuroscience y Psicología, Universidad de Cevadán, Spain (Sugranyes, Baeza); Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, Seoul, Republic of Korea (Ikwak, Hwang); Department of Psychiatry and Behavioral Sciences, University of California, San Francisco (Mathalon, Hamilton, Loewy, Roach); San Francisco Veterans Affairs Healthcare System, San Francisco, California (Mathalon, Hamilton, Roach); Department of Neuropsychiatry, Toho University School of Medicine, Tokyo, Japan (Katagiri, Mizuno, Nemoto); Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, Chicago, Illinois (Hooker, Haut); Department of Child and Adolescent Psychiatry, Psychiatric University Hospital Zurich, University of Zurich, Zurich, Switzerland (Smigielski); Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric University Hospital Zurich, University of Zurich, Zurich, Switzerland (Smigielski, Heereken, Rösler, Theodoridou); Department of Psychiatry, Columbia University, New York, New York (Colizatti); New York State Psychiatric Institute, New York (Colizatti); Child and Adolescent Mental Health Research Group, Institut de Recerca Sant Joan de Déu, Barcelona, Spain (Via, Dolz, Muñoz-Samons, Tor); Child and Adolescent Psychiatry and Psychology Department, Hospital Sant Joan de Déu, Barcelona, Spain (Via, Dolz, Muñoz-Samons, Tor); Department of Psychiatry, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China (Tang); Key Laboratory of Medical Neurobiology of Zhejiang Province, School of Medicine, Zhejiang University Hangzhou, Hangzhou, China (Tang); Center for Evolutionary Cognitive Sciences, Graduate School of Arts and Sciences, The University of Tokyo, Tokyo, Japan (Koike); The University of Tokyo Institute for Diversity and Adaptation of Human Mind, Tokyo, Japan (Koike, Kasa); Priority Centre for Brain and Mental Health Research, The University of Newcastle, Newcastle, Australia (Rasser, Schall); Priority Research Centre for Stroke and Brain Injury, The University of Newcastle, Newcastle, Australia (Rasser); University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland (Michel, Kaess, Kindler); Mental Health Research Center, Moscow, Russia (Lebedeva, Omelechenko, Tomyszew); Faculty of Social Sciences, University of Stavanger, Stavanger, Norway (Hegelstad); TIPs Centre for Clinical Research, Toho University, Stavanger, Norway (Hegelstad); Laboratory of Experimental Psychiatry, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico (de la Fuente-Sandoval, León-Ortiz, Moncada-Habib, Reyes-Madrigal); Maryland...
Psychiatric Research Center, University of Maryland School of Medicine, Baltimore (Waltz); Douglas Research Center, Montreal, Quebec, Canada (Mizrahi), McGill University, Department of Psychiatry, Montreal, Quebec, Canada (Mizrahi); Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York (Corcoran, Haas); Mental Illness Research, Education and Clinical Center (MIRECC), James J. Peters VA Medical Center, New York, New York (Corcoran); Clinic for Child and Adolescent Psychiatry, University Hospital of Heidelberg, Heidelberg, Germany (Resch); Department of Psychiatric Research, Diakoniehjemmet Hospital, Oslo, Norway (Tannes, Agatz); NORMENT, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway (Tannes, Agatz, Andreasen, Russberg, Varens, Westbye); PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo, Norway (Tannes); Faculty of Behavioural and Mental Health Sciences, Department of Clinical, Neuro and Developmental Psychiatry, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands (Lemmers-Jansen); Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (Agartz); Department of Psychosomatic Medicine and Addiction, University of Rehovot, Rehovot, Israel (Cani); United Kingdom (Allen); Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, United Kingdom (Allen, Baldwin, McGuire); Division of Psychiatry, University of Edinburgh, Edinburgh, United Kingdom (Birchwood, Jones, Harris, Lawrie, Vanezoglu); NHRI Maudsley Biomedical Research Centre, South London and Maudsley NHS Foundation Trust and King’s College London, London, United Kingdom (Baldwin); Department of Psychiatry, University of Basel, Basel, Switzerland (Borgwardt, Schmidt); Department of Psychiatry and Psychotherapy, University of Lübeck, Lübeck, Germany (Borgwardt); National Clinical Research Center for Mental Disorders and Department of Psychiatry, The Second Xiangya Hospital of Central South University, Changsha, China (Chen, He, Ma, Ouyang, Yuan); National Clinical Research Center for Geriatrics, Xiangya Hospital, Central South University, Changsha, China (Chen, Ouyang, Yuan); Department of Psychiatry, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts (Cho); Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, Australia (Cooper, Croyele, Pantelis, Velakoulis); Centre for Mental Health, Faculty of Health, Arts and Design, School of Health Sciences, Swinburne University, Melbourne, Australia (Croyele, Pantelis); Center for Clinical Intervention and Neuropsychiatric Research, Mental Health Centre Glostrup, University of Copenhagen, Glostrup, Denmark (Ekdrup, B. Y. Glenthoj, Kristensen, Sorensen); Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark (Ekdrup, B. Y. Glenthoj); Department of Child and Adolescent Psychiatry, Research Institute of Neuroscience, Hospital Clinic Barcelona, Fundació Clinic Recerca Biomèdia, Universitat de Barcelona, Barcelona, Spain (Fortea); Department of Psychiatry, Amsterdam University Medical Centre, Amsterdam, the Netherlands (de Haan); Arkin, Amsterdam, the Netherlands (de Haan); Department of Psychiatry and Psychotherapy, LVR-Hospital Cologne, Cologne, Germany (Heeren); Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin, Berlin, Germany (Heinrichs-Weiss, Schlagenhahn); Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland (Hub); Department of Child and Adolescent Psychiatry, Center of Psychosocial Medicine, University of Heidelberg, Heidelberg, Germany (Gener, Vargn); Department of Neuropsychiatry, Graduates School of Medicine, The University of Tokyo, Tokyo, Japan (Kasai); The International Research Center for Neurointelligence at The University of Tokyo Institutes for Advanced Study, The University of Tokyo, Tokyo, Japan (Kasai); Department of Neuropsychiatry, Seoul National University Hospital, Seoul, Republic of Korea (Kim, Kwon); Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea (Kim, Kwon); Department of Psychology, University of Idaho, Moscow, USA (Van de Velden); Beijing (Kuang, Schilling); Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada (Koppel); Department of Psychiatry, Institute of Mental Health, Singapore (Lee); Lee Kong Chian School of Medicine, National University of Singapore, Singapore (Lee); Telethon Kids Institute, The University of Western Australia, Perth, Australia (Lin); Department for Mental Health Research and Development, Division of Mental Health and Addiction, Vestre Viken Hospitalet Trust, Lier, Norway (Meller); Stavanger Medical Imaging Laboratory, Department of Radiology, Stavanger University Hospital, Stavanger, Norway (Oppdal); Haukeland University Hospital, Bergen, Norway (Somiya); Department of Psychiatry and Mental Health, Changsha, China (Ouyang, Yuan); Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia (Pantelis); Magnetic Resonance Imaging Core Facility, Institut d’Investigacions Biomèdiques August Pi Sunyer, Barcelona, Spain (Pariente); Department of Clinical Physiology, Nuclear Medicine and PET, Functional Imaging Unit, University of Copenhagen, Gostrup, Denmark (Raghava); Priority Research Centre Group Up Well, The University of Newcastle, Newcastle, Australia (Schall); Department of Psychological Science, University of California, Irvine (Schipffmann); Early Intervention in Psychosis Advisory Unit for South-East Norway, TIPS Sør-Ost, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway (Varens); Neuropsychiatry, The Royal Melbourne Hospital, Melbourne, Australia (Velakoulis); Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Faculty of Health Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands (Via); Neuropsychiatry, Herren); Department of Psychiatry and Behavioral Sciences, University of Minnesota, Minneapolis (Vinogradov); Department of Psychology, University of Oslo, Oslo, Norway (Westbye); Department of Psychiatry, Hamamatsu University School of Medicine, Hamamatsu City, Japan (Yamasue); School of Health Sciences, University of Manchester, Manchester, United Kingdom (Yung); Department of Psychology, Georgia State University, Atlanta (Turner); Center for the Neurobiology of Learning and Memory, Irvine, California (van Erp); Clinical Translational Neuroscience Laboratory, Department of Psychiatry and Human Behavior, University of California, Irvine (van Erp); Imaging Genetics Center, Mark and Mary Stevens Institute for Neuroimaging and Informatics, Keck School of Medicine of USC, University of Southern California, Los Angeles (Thompson).

Author Contributions: Drs Jalbrzikowski and Hernaas had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Jalbrzikowski, Hernaas. Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Jalbrzikowski, Hernaas. Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Jalbrzikowski, Hernaas. Administrative, technical, or material support: Jalbrzikowski, Hayes, Catalano, Hernaas.


Conflict of Interest Disclosures: Dr Fusar-Poli has received grants from Lundbeck; personal fees from Angelima Pharma and Menarini Group; and nonfinancial support from Boehringer Ingelheim. Dr Uhlhaas has received grants from Lundbeck and Eli Lilly UK. Dr Takahashi has received personal fees from Toyama Hospital, Taikoyama Hospital, Saiseikai Toyama Hospital, and Greenhills Walakusa Hospital. Dr Mathalon has served as a consultant to Boehringer Ingelheim, Cadent Therapeutics, Syndesi Therapeutics, and Recognify. Drs Via and Dolz have received personal fees from Janssen-Cilag. Dr Koike has received grants from Agency for Medical Research and Development, Japan Society for the Promotion of Science, the Naito Foundation, and Takeda Science Foundation. Dr Andreassen has received personal fees from Lundbeck and Sunovion and has served as a consultant for HealthLytix. Dr Baeya has received personal fees from Angelima Pharma, Janssen Pharmaceuticals, and Otsuka-Lundbeck. Dr Chee has served as a sleep consultant for the AIA Vitality Program. Dr Ekdrup has received personal fees for serving on advisory boards from Eli Lilly Denmark, Janssen-Cilag, Lundbeck, and Takeda and has received lecture fees from Bristol Myers Squibb, Otsuka Pharma Scandinavia, Eli Lilly and Company, Boehringer Ingelheim Denmark, and Lundbeck. Dr Fortea has received honoraria from Otsuka-Lundbeck. Dr Birte Glenthoj is the leader of a Lundbeck Foundation Centre of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research, which is partially funded by an independent grant from the Lundbeck Foundation and partially funded by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen, and other foundations. Dr Kaess has received grants from German Federal Ministry of Education and Research, Swiss National Science Foundation, German Research Foundation, Dietmar Hoff Foundation, Baden-Wuerttemberg Foundation, and National Health, Medical, and Research Council. Dr Kasai has received grants from Novartis, Astellas, Merck Sharp and Dohme, Eli Lilly and Company, Dainippon-Sumitomo Corporation, Eiisai, Otsuka, Shionogi, Ono, Tanabe-Mitsubishi, and Takeda.
personal fees from Otsuka, Fuji-Film, Yoshitomi, Kyowa, Jansen Pharmaceuticals, Astellas, Meiji Sekia Pharma, Sumitomo Dainippon Pharma, and Takeda, and serves on the funding committees of Takeda Science Foundation and Astellas. Dr. Kindler has received grants from the Swiss National Science Foundation. Dr. Kristensen has received grants from Lundbeck Foundation. Dr. Lawrie has received personal fees from Jansen Pharmaceuticals and Sunease. Dr. Le Dainh-Kritz has received personal fees from Jansen Pharmaceuticals. Dr. Loewy has received grants from National Institute of Mental Health and California Mental Health Services Authority. Dr. Nemoto has received grants from Otsuka as well as personal fees from Astellas, Eisai, Jansen Pharmaceuticals, Meiji Sekia Pharma, Sumitomo Dainippon Pharma, and Takeda. Dr. Pantelis has received grants and personal fees from Lundbeck Foundation. Dr. Reyes-Madrigal has received speaker fees from Jansen (Johnson & Johnson). Dr. Rüssler is supported by the Zurich Program for Sustainable Development of Mental Health Services. Dr. Suzuki had received personal fees from Nakagawa Hospital. Ms. Tor has received personal fees from Fundación Alcudina and is an unpaid scientific collaborator for P1vital Products. Dr. Vinogradov served as a member of an advisory board for Alkermes and is an unpaid scientific collaborator for Science Inc. Dr. Hennas has received consulting fees from Pivital Products. No other disclosures were reported.

**Funding/Support:** Dr. Jablonskiowski has received grant K01 MH112774 from the National Institute of Mental Health. Dr. Hayes has received grants from the University of Pittsburgh Medical Center. Drs. Wood, Amninger, Bartholomew, McGorry, Nelson, and Yung have received funding from the Colonial Foundation. Drs. Wood, McGorry, and Yung have received grant 566529 from the National Health and Medical Research Council. Dr. Wood has received Clinical Career Development Award 359223 from the National Health and Medical Research Council. Dr. Nordholm has received grants R25-A2701 and R287-2018-1485 from the Lundbeck Foundation and grants from the Mental Health Services Capital Region of Denmark. Dr. Zhou has received grants from the Yong Loo Lin School of Medicine at the National University of Singapore. Drs. Kasai and McGuire and have received grant UK G0700995 from the UK Medical Research Council. Dr. Ulfhåas has received grant MR/L01689/1 from the UK Medical Research Council. Dr. Suganenyes has received Young Investigator Award grant 26731 from the Brain and Behavior Research Foundation, grants from the Spanish In-Di state program, grants from the ISCIII-Subdirección General de Evaluación, grant PI18/00976 from the European Regional Development Fund, grant SLT06/170/0362 from the Government of Catalonia (Programa PERIS Salut Mental), grants from the Alicia Koplowitz Foundation, and grants from the Fundació Clinic Recerca Biomèdica (Ajut a la Recerca Pons Bartran). Dr Mathalon has received grants from the Brain and Behavior Research Foundation and grant R01 MH076989 from the National Institute of Mental Health. Dr Hooker was supported by grant R01 MH076246 from the National Institutes of Health. Dr Colbibazi has received grants ST23MH15144 and K23 MH05603 from the National Institute of Mental Health as well as grants from the Brain and Behavior Research Foundation, Sackler Institute, Herbert Irving Scholar Award, and Columbia University Bodini Fellowship. Dr Tang has received grant S1870157 from the National Science Foundation of China. Drs Koike and Kasai have received grants JP20dm0207004 and JP20dm0207069 from the Japan Agency for Medical Research and Development. Dr. Koike has received grant JP18BK07550 from the Japan Society for the Promotion of Science KAKENHI. Dr Lebedeva and Mr Tornyovsh were supported by grant 20-013-00748 from the Russian Foundation for Basic Research. Dr. de Fuentes-Sandoval was supported by grants 182279 and 261895 from the Consejo Nacional de Ciencia y Tecnología, grants from CONACYT’s Sistema Nacional de Investigadores, and grant 2R1 MH117434 from the National Institutes of Health. Dr Waltz has received grant SROI1H11301 from the National Institute of Mental Health. Dr Mizrahi has received grants R01MH110043 and R01MH113564 from the National Institute of Mental Health and grants from the Brain and Behavior Research Foundation and Canadian Institutes of Health Research. Dr Corcoran has received grants R01MH107585 from the National Institutes of Health. Dr Tannnes has received grants 288083 and 223273 from the Research Council of Norway and grant 2019069 from the South-Eastern Norway Regional Health Authority. Dr Amninger has received Senior Research Fellowship FO0044, grant 108099 from the National Health and Medical Research Council. Dr Andreasen has received grants 223273 and 283798 from the Research Council of Norway as well as grants from K. G. Jebsen Stiftelsen and UIO: Life Science. Ms Atkinson has received grants from the University of Edinburgh. Dr Baeza has received grants INT09/0021, PIT51349, PIT50444, and PIT50242 from the Instituto de Salud Carlos III. Ms Baldwin has received funding from the National Institute for Health Research Maudsley Biomedical Research Centre studentship. Dr Borgwardt has received grants from the SYNCHIZ project under the ERA-NET Horizon 2020 program. Drs Chen and Lee received grant NMRC/TCR/003/2008 from the National Medical Research Council Translational and Clinical Research Flagship Programme. Dr Chen has received grant NMRC/STAR/0015/2013 from the National Medical Research Council. Dr Cropyler has received a career development grant from 117370 and project grant 1065742 from the National Health and Medical Research Council. Dr Dolz has received grants PITI0268 and PIT101509 from the Instituto de Salud Carlos III and a grant from the Alicia Koplowitz Foundation. Dr Louise Gentjah was supported by the Tyyg Foundation and Danish Research Council. Dr Birte Gentjah was supported by the Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research. Mr Harris has received grants from the Wellcome Trust. Dr Kasai has received grants JP17bdn0207004 and JH17007001 from the Japan Agency for Medical Research and Development and grants JP16H06395, JP16H06399, JP16H06270, and 20H03596 from the Japan Society for the Promotion of Science KAKENHI. Dr Klauing has received grants from the National Institute of Mental Health, Dr Kwon has received grant 2017M3C7A1029610 from the National Research Foundation of Korea. Dr Lin was supported by grants 1148793 from the Australian National Health and Medical Research Council. Dr Loewy has received grants K23MH08618 and R01MH08051 from the National Institute of Mental Health. Drs McGorry and Yung have received grant 350241 from the National Health and Medical Research Council. Dr Nelson has received Career Development Grant 1027532, Senior Fellowship grant 1027741, and project grant 1027741 from the National Health and Medical Research Council. Dr Oppedal has received postdoctoral scholarship grant 91252 from the Western Norway Regional Health Authority. Dr Pantelis has received Senior Principal Research Fellowship grant 1105823 and 13 Investigator grant 1196028 from the National Health and Medical Research Council as well as Distinguished Investigator Award 18722 from the Brain and Behavior Research Foundation. Dr Rössler has received grants from the Zurich Program for Sustainable Development of Mental Health Services. Dr Salisbury has received grant R01 MH13533 from the National Institute of Mental Health. Dr Sasabayashi has received grant JP18K15509 from the Japan Society for the Promotion of Science KAKENHI. Dr Schall has received grant S569259 from the National Health and Medical Research Council of Australia. Dr Schiffman has received grants from the Maryland Department of Health and Mental Health, Behavioral Health Administration through the Maryland Center of Excellence on Early Intervention Program, grant 14-1377/0149 from the Wellcome Trust, and grant 1027532, Senior Research Fellowship grant 1105823 and project grant 1027741 from the National Health and Medical Research Council. Dr Cropley has received grants SROI1H1137 from the National Institute of Health. Dr Suzuki has received grants J02H03598 from the Japan Society for the Promotion of Science KAKENHI and grant JP19dk0307069 and 0203 from the Japan Agency for Medical Research and Development. Ms Tor has received grants PI170261 and PI1605509 from the Instituto de Salud Carlos III. Dr Westlye has received grant 30076 from the Research Council of Norway, grant 2019010 from the South-Eastern Norway Regional Health Authority, and European Union’s Horizon 2020 Research and Innovation Program grant 802998 from the European Research Council. Dr Yung has received Principal Research Fellowship grant GNT1136829 from the National Health and Medical Research Council and Senior Research Fellowship grant 566593 from the National Health and Medical Research Council. Dr Turner has received grant SROI1H094524 from the National Institutes of Health.

**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**REFERENCES**


---

764 JAMA Psychiatry July 2021 Volume 78, Number 7

© 2021 American Medical Association. All rights reserved.

jamapychiatry.com
Association of MRI Measures With Psychosis Onset in Individuals at Clinical High Risk for Developing Psychosis

Original Investigation Research

Individuals.

First-episode psychosis, and ultra-high-risk resonance imaging study of chronic schizophrenia, Hippocampal and amygdala volumes according to psychosis.


38. Radua J, Vieta E, Shinohara R, et al. ENIGMA Consortium Collaborators. Increased power by harmonizing structural MRI site differences with the...


