INTERNATIONAL REVIEW OF PSYCHIATRY
2019, VOL. 31, NOS. 5–6, 523–542
https://doi.org/10.1080/09540261.2019.1670624

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Late-onset psychosis and very-late-onset-schizophrenia-like-psychosis: an updated systematic review

Y. N. Suen[a]*, Stephanie M. Y. Wong[a]*, Christy L. M. Hui[a], Sherry K. W. Chan[a,b], Edwin H. M. Lee[a], Wing C. Chang[a,b] and Eric Y. H. Chen[a,b]

[a]Department of Psychiatry, University of Hong Kong, Hong Kong SAR, China; [b]State Key Laboratory of Brain and Cognitive Sciences, University of Hong Kong, Hong Kong SAR, China

ABSTRACT

Psychotic disorders have long been known to be a condition that peaks during adolescence and early adulthood. A considerable proportion of patients have their first onset at or after the age of 40, but little is known about this population. The current systematic review examined the clinical presentation of late-onset psychosis (LOP) and very-late-onset-schizophrenia-like psychosis (VLOSLP) with focus on their psychopathological, neuropsychological, neurobiological, psychosocial and psychological correlates. A systematic search of studies published from 2000 to 2019 from *Cochrane Library, Pubmed, Medline, Embase, PsycINFO, and Scopus* yielded 27 original studies that were included in this review. Results revealed there is a dearth of empirical research on the conditions in the current literature and inconsistencies in the findings reported may be associated with the lack of uniformity in the definitions for LOP and VLOSLP. Future research on the topic shall (i) specify the onset age criteria for LOP and VLOSLP; (ii) study the conditions independently; (iii) involve a larger sample size, and iv) account for potential confounding variables. A comprehensive evaluation of the risks and benefits of pharmacological treatment may also be needed.

ARTICLE HISTORY
Received 29 July 2019
Accepted 17 September 2019

KEYWORDS
Late-onset psychosis; psychopathology; neurobiology; neuropsychology; psychosocial

Background

Psychosis is one of the most functionally disruptive mental health conditions, predominantly characterised by delusions, hallucinations, and functional impairments (Insel, 2010; Rossler, Salize, van Os, & Riecher-Rossler, 2005). When left unidentified and untreated, the condition can place significant impacts on the individual and burden on a society's resources and overall mental wealth (Beddington et al., 2008).

Most studies on psychosis focus on patients with early-onset psychosis (EOP; i.e. onset before the age of 40) as the condition usually first manifests in adolescence or early adulthood (Jordan et al., 2018). However, some studies have reported as many as 20% of patients with schizophrenia (SZ) have their first onset at or after the age of 40, i.e. late-onset psychosis (LOP) (Maglione, Thomas, & Jeste, 2014), and at least 1% of the elderly population presents SZ (Jeste, 1993). Cases of LOP had been documented since the 1940s (Bleuler, 1943), yet much fewer empirical studies had been conducted to examine the condition and its relationship with EOP due to its low prevalence. It was not until two decades ago that a group of researchers and experts (Howard, Rabins, Seeman, & Jeste, 2000) had put forward an international consensus on the criteria, which defines LOP as psychosis with onset after the age of 40 and very-late-onset-schizophrenia-like psychosis (VLOSLP) as psychosis with onset after the age of 60.

Apart from the cut-off for onset age, questions have also been raised concerning the clinical validity of LOP and VLOSLP (Sachdev, Mohan, Taylor, & Jeste, 2015). A diagnosis of SZ and other psychotic disorders was exclusively given to those with onset before the age of 45 in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (American Psychiatric Association, 1980). It was not until DSM-III-R that a 'late-onset' specifier was added, and DSM-IV that age of onset was removed as one of the defining criteria for psychotic disorders (American Psychiatric Association, 1987, 1994). Although LOP and VLOSLP are generally

CONTACT Y. N. Suen suenyn@hku.hk Department of Psychiatry, University of Hong Kong, 2/F New Clinical Building, Queen Mary Hospital, Pokfulam Road, Hong Kong, China
*These authors equally contributed to this work.

viewed as subtypes of psychotic disorders, some critical differences exist in their clinical presentation as compared with the early-onset type. For instance, researchers have generally found a female preponderance, lower genetic risk (reflected by a lower incidence of family history of psychosis), and higher rates and more severe paranoid symptoms and persecutory delusions in LOP and VLOSLP patients (e.g. Chen, Selvendra, Stewart, & Castle, 2018; Howard et al., 1997; Meesters et al., 2012). Furthermore, given the higher risk of dementia in LOP and VLOSLP reported in some studies as opposed to EOP and healthy controls (HC), the conditions had also been viewed as prodromal symptoms or states of neurodegenerative disorders (Cohen, 2018; Kwak, Yang, & Koo, 2015; Van Assche et al., 2019). This argument nonetheless remains largely debated as other researchers had also found that cognitive changes in LOP patients had greater resemblance to EOP and HC versus neurodegenerative diseases (Palmer et al., 2003) and that the cognitive deficits in VLOSLP are non-progressive in nature (Brodaty, Sachdev, Koschera, Monk, & Cullen, 2003).

What constitutes the two late-onset conditions remain inconclusive. To date, few systematic reviews had been conducted on the topic, and the majority of which tended to focus on specific aspects of the conditions (e.g. psychopathological, neurobiological, neuropsychological, psychological) or LOP and VLOSLP in separation (Brunelle, Cole, & Elie, 2012; Essali & Ali, 2012; Rajji & Mulsant, 2008; Stafford, Howard, & Kirkbride, 2018; Van Assche, Morrens, Luyten, Van de Ven, & Vandenbulcke, 2017). Much inconsistencies in the existing literature were generally reported. To consolidate existing knowledge in the area, the current systematic review aims to identify and analyse original studies on LOP and VLOSLP and put forward a more comprehensive picture of the conditions encompassing the following four key domains: psychopathology, neuropsychology, neurobiology, and psychosocial and psychology.

Materials and methods

Search strategy

The current systematic literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Moher et al., 2015). Six databases were searched to identify studies on LOP and VLOSLP published between January 2000 and March 2019: *Cochrane Library, Pubmed, Medline, Embase, PsycINFO, and Scopus*. The following combination of keywords was applied to identify relevant studies (limited to title and abstract): ("Psychosis" OR "Psychos*" OR "Psychotic" OR "Delusion*" OR "Schizophrenia-like psycho*" OR "Paraphreni*" OR "Schizophrenia" OR "Schizophrenic") AND ("Late-onset" OR "LOP" OR "VLOSLP" OR "Very late-onset" OR "Late-life" OR "Later-life").

Selection criteria

After removing duplicates and irrelevant studies, the titles and abstracts of the publications were screened for eligibility against the following criteria:

- **The study focused on LOP or VLOSLP, with a defined onset age criterion of 40 years or above**. This criterion for LOP is based on the international consensus put forwarded by Howard's group (Howard et al., 2000). Considering the wide variability in cut-off age used to define the conditions in existing studies, a single cut-off was adopted instead of the recommended classifications (i.e. between 40 and 60 years for LOP and after 60 years for VLOSLP).
- **The study was an original empirical study published in English.** Only empirical research with clearly described methodologies and prospective quantitative data are included to increase the confidence and generalisability of the summarised findings. Grey literature, case studies, case note and chart review studies, autopsy studies, register-based studies, commentaries, and any form of reviews were excluded.
- **The study was published after the year 2000.** Since the definitions for LOP and VLOSLP had not been standardised until the international consensus group meeting in the year 2000, only studies published after that were included.
- **Participants in the study met the diagnostic criteria for schizophrenia or other psychotic disorders of the DSM (including DSM-III, DSM-III-R, DSM-IV, and DSM-IV-TR) or the International Classification of Diseases (ICD; including ICD-9 and ICD-10).** This inclusion criterion was applied to ensure the results of the current review will have implications for future clinical and research work with LOP and VLOSLP patients.
- **The current age of all participants is specified.** This information is particularly relevant in reviewing studies about onset age, as the duration of

Table 1. Main findings of the 27 included articles, sorted by domains.

Domain	Study, country	Sample	Age of onset cut-off/ range	DOI	Mean age	Main findings
Psychopathological	Brichant-Petitjean et al. (2013), France	LOS outpatients ($n = 25$); & EOS outpatients ($n = 44$); & Age-matched HC ($n = 23$)	LOS: 45-65	LOS = EOS LOS: 9.12 EOS: 12.25	LOS > EOS LOS: 50.9 EOS: 35.4	• LOS scored lower than EOS on total and the positive, negative, and general subscales of PANSS.
	Brodaty et al. (2003), Australia	VLOSLP outpatients ($n = 27$); & Age-matched HC ($n = 34$) [a]*authors referred to this group as LOS*	LOS: ≥50	VLOSLP with dementia at 5 years: 12.4 VLOSLP without dementia at 5 years: 7.8 [a]*no comparison and baseline data available*	VLOSLP with dementia at 5 years: 70 VLOSLP without dementia at 5 years: 67	• Of the 7 VLOSLP, 1 met the DSM-IV criterion A for SZ, 5 had delusions or hallucinations, 1 had grandiose ideation and (probable) psychosis at 5-year follow-up.
	Hanssen et al. (2015), Netherlands	LOP ($n = 24$); & VLOSLP ($n = 28$); & EOP ($n = 286$); & HC (N = 290)	LOP: 40-59 VLOSLP: ≥60	LOP = VLOSLP = EOP LOP: 9.25 VLOSLP: 6.61 EOP: 4.65	VLOSLP > LOP > EOP LOP: 58.13 VLOSLP: 75.68 EOP: 27.37 [a]*HC matched with all psychosis groups*	• VLOSLP showed more positive and disorganised symptoms than LOP and EOP, but after controlling for confounding variables (sex, education years, and disorganisation factor), only the VLOSLP-EOP difference on positive symptoms remained.
	Huang and Zhang (2009), Taiwan	Long-stay LOS inpatients ($n = 23$); & Long-stay elderly EOS inpatients ($n = 29$)	LOS: >40	LOP < EOP LOP: 16.7 EOP: 38.2	LOS = EOS LOS: 65.3 EOS: 66.0	• NSD on all clinical psychopathological measures, except more thought disorder symptoms in LOS.
	Hussein et al. (2012), Egypt	LOP ($n = 50$; 70% paranoid SZ, 14% schizoaffective disorder, 12% delusional disorder, 4% undifferentiated SZ), & Late-onset other psychoses ($n = 29$; 70% psychosis due to dementia, 20% mood disorder with psychotic symptoms, 10% psychosis due to medical condition)	LOP: >50	LOP > LOOP LOP: 14.06 LOOP: 2.86	LOP < LOOP LOP: 69.5 LOOP: 72.5	• LOP showed more positive symptoms and less general psychopathology than late-onset other psychosis, though NSD in negative symptoms and total PANSS score. • More bizarre delusions in LOP versus more simple delusions in late-onset other psychosis. • LOP experience more types of hallucination and at greater intensity than late-onset other psychosis. More auditory hallucination in LOP, versus more visual hallucination in late-onset other psychosis with dementia.
	Mason et al. (2013), United Kingdom	LOS ($n = 34$) & EOS ($n = 235$)	LOS: >40	LOS < EOS LOS: 5.5 EOS: 9	LOS > EOS LOS: 56.0 EOS: 36.0	• Delusions were present in most patients in both LOS and EOS (LOS = 82%, EOS = 85%). • More EOS experienced both hallucinations and delusions when compared with LOS • NSD on all PANSS scores, though LOS had lower PANSS positive score when age was matched, and higher PANSS global score when DOI was matched. • For those with delusions: LOS showed greater degrees of suspiciousness/ persecution, belief conviction, unusual thought content, and lower judgment and insights. All except unusual thought content remained higher in LOS after DOI was matched, and only unusual thought content remained higher in LOS when age was matched.

(*continued*)

Table 1. Continued.

Domain	Study, country	Sample	Age of onset cut-off/ range	DOI	Mean age	Main findings
						• For those with hallucination: 50% LOS heard 'whispers' versus 24% in EOS; more EOS reported voices as louder than or equal to voice-level.
	Reeves et al. (2002), United Kingdom	VLOSLP ($n = 26$)	VLOSLP: >60	VLOSLP (median): 13	VLOSLP (median): Female: 78.0 Male: 77.5	• Most patients exhibited paranoid symptoms (38%) and persecutory delusions (31%), followed by hallucinations (15%). No thought disorder or negative symptoms present. • Over half of the patients showed no insights (62%), some showed partial insight (35%), and one showed complete insight. • Males had more compulsory hospital admissions and more lost to follow-up case compared to females.
	Sato et al. (2004), Germany	Neuroleptic-naïve, first episode, and first-admission LOS ($n = 55$), & EOS ($n = 418$)	LOS: 41-60	LOS = EOS LOS: 3.1 EOS: 2.2 [a]*from onset to first admission*	LOS > EOS LOS: 50.0 EOS: 27.8	• Significant effect of onset age on psychopathological symptoms, but not gender, at both admission and discharge. • LOS scored higher on systematic persecutory delusion, while EOS scored higher on affective flattening/social withdrawal (even when controlling for other potential sources of secondary negative symptoms), at both admission and discharge. • EOS scored marginally higher than LOS on alogia/mutism at admission but not at discharge.
	Vahia et al. (2010), United States	LOS ($n = 110$); EOS ($n = 744$), & HC ($n = 359$)	LOS: ≥40	LOS < EOS ([a]significance not tested) LOS: 9.4 EOS: 28.1	LOS > EOS LOS: 57.6 EOS: 51.0	• No LOS-EOS difference in proportion of patient with paranoid SZ (LOS = 36%, EOS = 33%). • LOS scored lower on PANSS positive and general psychopathology than EOS. NSD on their PANSS negative, HAM-D, and PDS. • After adjusting for severity of negative and deficit symptoms and controlling for DOI, all LOS-EOS differences remained significant except PANSS positive symptoms.
	Wake et al. (2016), Japan	LOS ($n = 19$); HC matched for LOS ($n = 10$), & HC matched for EOS ($n = 27$)	LOS: ≥40	LOS > EOS LOS: 8.2 EOS: 5.3	LOS > EOS LOS: 55.2 EOS: 33.8	• NSD between LOS and EOS in BPRS, PANSS, and WAIS-R.
Neuropsychological	Brichant-Petitjean et al. (2013), France	LOS outpatients ($n = 25$); & EOS outpatients ($n = 44$); & Age-matched HC ($n = 23$)	LOS: 45-65	LOS = EOS LOS: 9.12 EOS: 12.25	LOS > EOS LOS: 50.9 EOS: 35.4	• LOS scored higher than EOS on forward and global DST, RCFT at T1 (delay), and phonemic VFT, but slower to complete RCFT. • LOS scored lower than HC on backward and global DST and both semantic and phonemic VFT. Scores were comparable on RCFT but LOP were slower to complete.

(*continued*)

Table 1. Continued.

Domain	Study, country	Sample	Age of onset cut-off/ range	DOI	Mean age	Main findings
	Brodaty et al. (2003), Australia	VLOSLP outpatients ($n = 27$); & Age-matched HC ($n = 34$) [a]*authors referred to this group as LOS*	LOS: $\geq$ 50	VLOSLP with dementia at 5 years: 12.4 VLOSLP without dementia at 5 years: 7.8 [a]*no comparison and baseline data available*	VLOSLP with dementia at 5 years: 70 VLOSLP without dementia at 5 years: 67	• At baseline, NSD in cognitive function between VLOSLP and HC. • At 5 years: greater decline in cognitive level in VLOSLP. • Dementia at 5 years: VLOSLP (9/19 patients) > HC (none) • VLOSLP with dementia at 5 years were older, had lower SES, longer DOI, worse functioning (IADL and GAF).
	Chen et al. (2013), China	LOS inpatients ($n = 20$); & Age-matched HC ($n = 17$)	LOS: 40-60	LOS: 2.9	LOS: 46.9	• LOP had worse performance on the WSCT (fewer categories and more errors), DST (fewer numbers), and TMT (significant longer time to complete) compared with HC.
	Girard et al. (2011), Canada	LOP inpatients ($n = 15$); & Unmatched elderly EOS inpatients ($n = 17$), & Age-, gender-, & education-matched HC for LOP ($n = 11$) & for EOS ($n = 11$)	LOP: $\geq$50 EOS: <40	LOP < EOS LOP: 4.78 EOS: 36.40	LOP > EOS LOP: 75.6 EOS: 65.5	• NSD in cognitive deficits between LOP and EOS, but visual inspection of scores showed more executive deficits (more intrusion, lower cognitive flexibility) in LOP, while greater difficulties in learning or retrieving new information due to prior learning are seen in EOS (proactive interference). • NSD in cognitive functions between LOP and HC when adjusting with age and education level, but more deficits in EOS (episodic memory, semantic fluency, and executive function) than HC. • More LOP met criteria for dementia when compared with EOS (3/15 vs. 1/17), though the majority of both groups presented significant cognitive deficits without dementia.
	Hanssen et al. (2015), Netherlands	LOP ($n = 24$); & VLOSLP ($n = 28$); & EOP ($n = 286$); & HC ($n = 290$)	LOP: 40-59 VLOSLP: $\geq$60	LOP = VLOSLP = EOP LOP: 9.25 VLOSLP: 6.61 EOP: 4.65	VLOSLP > LOP > EOP LOP: 58.13 VLOSLP: 75.68 EOP: 27.37 [a]*HC matched with all psychosis groups*	• NSD between groups on general IQ, memory, attention, and executive functions. • NSD on CAMCOG between VLOSLP and LOP. However, VLOSLP performed better on overall cognitive function than LOP after adjusting for sex, education years and remission state, but worse on CPT (i.e. attention accuracy task) when accounting for confounding variables.
	Harris et al. (2014), Australia	Very-late onset delusional disorder outpatients ($n = 19$); & Unmatched AD outpatients ($n = 20$)	Very-late onset delusional disorder: >65	VLODD: 2.89 AD: n/s [a]*data missing for 1 VLODD patient; (n.b. wide DOI range: 3 months - 20 years)*	LODD = AD VLODD: 83.5 AD: 79.6	• NSD between groups on MMSE scores, estimated premorbid intellectual functions, and immediate recall measures. • NSD between groups and age-matched norms on immediate recall. • Very-late-onset delusional disorder had more impairments in conceptual reasoning, object recognition, processing speed, naming, divided attention, and working memory.

(*continued*)

Table 1. Continued.

Domain	Study, country	Sample	Age of onset cut-off/ range	DOI	Mean age	Main findings
						• AD had more impairments in episodic memory and delay recall.
	Huang and Zhang (2009), Taiwan	Long-stay LOS inpatients ($n = 23$); & Long-stay elderly EOS inpatients ($n = 29$)	LOS: >40	LOP < EOP LOP: 16.7 EOP: 38.2	LOS = EOS LOS: 65.3 EOS: 66.0	• Both LOS and EOS had poor cognitive and general functioning and poor global outcomes.
	Hussein et al. (2012), Egypt	LOP ($n = 50$; 70% paranoid SZ, 14% schizoaffective disorder, 12% delusional disorder, 4% undifferentiated SZ), & Late-onset other psychoses ($n = 29$; 70% psychosis due to dementia, 20% mood disorder with psychotic symptoms, 10% psychosis due to medical condition)	LOP: >50	LOP > LOOP LOP: 14.06 LOOP: 2.86	LOP < LOOP LOP: 69.5 LOOP: 72.5	• Late-onset other psychosis had poorer cognitive function than LOP. • LOP had more cognitive impairments than the norm according to Egyptian sample (on memory, apraxia, abstract, and perception).
	Laks et al. (2006), Brazil	LOS outpatients ($n = 13$)	LOS: >50	LOS: 6.69	LOS: 66.1	• LOS scored lower than the elderly Brazilian norm on MMSE, but NSD on CAMCOG and PFAQ at baseline and 1-year follow-up. • NSD in scores on MMSE, CAMCOG, PFAQ, and NPI between baseline and 1-year follow-up.
	Moore et al. (2006), United Kingdom	VLOSLP ($n = 29$); Very-late-onset depression ($n = 30$), & Matched HC for VLOSLP ($n = 30$)	VLOSLP: >60	VLOSLP = Very-late-onset depression VLOSLP: 2.88 Very-late-onset depression: 1.66	VLOSLP = Very-late-onset depression VLOSLP: 76.9 Very-late-onset depression: 77.1	• Both VLOSLP and very-late-onset depression had lower scores on estimated intelligence and backward DST (in WAIS) and memory items on the mentalising tasks. • VLOSLP committed more errors than HC in mentalising tasks involving deception. • NSD in mentalising tasks involving false beliefs, PRT, and ASQ internality and stability dimensions. • All groups were more likely to make more internal and global attributions to positive events and rate them with greater stability. • Very-late-onset depression made less global attributions for positive events than VLOSLP and HC, but both groups made more global attributions for negative events than HC.
	Palmer et al. (2003), United States	LOP outpatients ($n = 37$); EOP ($n = 71$); Probable AD with psychosis ($n = 67$); Probable AD with mild cognitive impairment with psychosis ($n = 72$), & HC ($n = 56$)	LOP: ≥45	n/s	N/A [a]*AD group older than others; LOP age not compared with EOP, though is used as a covariate in analysis*	• NSD in cognitive performance (MMSE and DRS) over periods of 1 and 2 years between LOP, EOP, and HC. • AD with psychosis and mild cognitive impairment showed significantly more declines in MMSE and DRS compared with LOP, as well as EOP and HC.

(*continued*)

Table 1. Continued.

Domain	Study, country	Sample	Age of onset cut-off/ range	DOI	Mean age	Main findings
						• Similar findings found in older age participants, i.e. 60-69 and 70-79 age groups. • Similar findings found in LOP with recent onset (onset within 1 year).
	Reeves et al. (2002), United Kingdom	VLOSLP ($n = 26$)	VLOSLP: >60	VLOSLP (median): 13	VLOSLP (median): Female: 78.0 Male: 77.5	• 23% developed cognitive impairments since initial diagnosis.
	Smeets-Janssen et al. (2013), Netherlands	LOS ($n = 15$); EOS ($n = 15$), & Age- & gender-matched HC for LOS ($n = 30$)	LOS: ≥40	LOS < EOS LOS: 20.4 EOS: 37.7	LOS = EOS LOS: 67.3 EOS: 65.5	• EOS showed worse performance on theory-of-mind when compared with LOS and HC. LOS slightly, insignificantly lower score on Hinting Task than HC. • NSD between LOS and EOS on PANSS, MMSE, FAB, or estimated premorbid intelligence.
	Vahia et al. (2010), United States	LOS ($n = 110$); EOS ($n = 744$), & HC ($n = 359$)	LOS: ≥40	LOS < EOS ([a]significance not tested) LOS: 9.4 EOS: 28.1	LOS > EOS LOS: 57.6 EOS: 51.0	• LOS and EOS scored lower than HC on all cognitive measures. • LOS scored higher than EOS on DST (processing speed), WCST (mental flexibility), CVLT (verbal memory), and Block Design task (perceptual-organisation ability). • After adjusting for severity of negative and deficit symptoms and controlling for DOI, all LOS-EOS differences remained significant except WCST, and CVLT.
	Van Assche et al. (2019), Belgium	VLOSLP ($n = 57$); AD with Psychosis ($n = 35$), & Dementia with Lewy Bodies ($n = 49$)	VLOSLP: >60	n/s	VLOSLP = AD with Psychosis = Dementia with Lewy Bodies VLOSLP: 79.3 AD with Psychosis: 78.8 Dementia with Lewy Bodies: 76.2	• Processing speed and executive function comparably impaired among the three groups. • AD with Psychosis showed more strongly reduced learning and consolidation skills, whereas Dementia with Lewy Bodies was associated with more prominent visuo-constructive deficits.
	Zakzanis et al. (2003), Canada	LOS outpatients ($n = 32$), & AD ($n = 32$)	LOS: ≥45	LOS > AD LOS: 6.9 AD: 3	AD > LOS (age-adjusted) LOS: 57.8 AD: 78.8	• CVLT long-delay, short-delay, and WAIS-III Similarities best discriminated LOS patients from AD. • WAIS-III Block Design had the lowest discriminability value.
	Zakzanis et al. (2001), Canada	LOS inpatients ($n = 32$) Formal thought disorders patients ($n = 12$)	LOS: ≥45	N/A LOS: 13 Formal thought disorders patients: N/A (due to nature of disease and unreliable recall from relatives)	LOS = Formal thought disorders patients LOS: 57.8 Formal thought disorders patients: 61.6	• Formal thought disorders scored significantly less than LOS on WCST and VFT, though the tests cannot reliably discriminate between these two groups. • LOS had lower DST score.

(*continued*)

Table 1. Continued.

Domain	Study, country	Sample	Age of onset cut-off/ range	DOI	Mean age	Main findings
Neurobiological	Barak et al. (2002), Israel	VLOSLP inpatients and outpatients ($n = 21$); & Age- and gender- matched long-stay EOS inpatients ($n = 21$)	VLOSLP: >70	EOS > VLOSLP EOS: long-stay (DOI n/s) VLOSLP: 46.5 ± 9 days [a]*duration of hospital stay*	LOS = EOS (matched) VLOSLP: 78.1 EOS: 76.7	• Cerebellar ventral-to-brain ratio (VBR): VLOSLP > EOS • No differences were found on the VBR of frontal horn, level of cortical atrophy, and periventricular white matter leukoencephalopathy.
	Chen et al. (2013), China	LOS inpatients ($n = 20$); & Age-matched HC ($n = 17$)	LOS: 40-60	LOS: 2.9	LOS: 46.9	• LOS showed reduced FA in left parietal lobe and right posterior cingulum and more cognitive deficits when compared with HC. • Reduced FA and cognitive deficits not correlated with PANSS scores, antipsychotic dosages, or any sociodemographic variable.
	Jones et al. (2005), United Kingdom	VLOSLP ($n = 14$) & HC ($n = 14$)	VLOSLP: >60	VLOSLP: 1.3	VLOSLP: 78.1	• NSD in FA and MD measures between VLOSLP and HC within the fibre tract. • FA and MD measures are associated with age.
	Rabins et al. (2000), United States	LOS ($n = 14$); Late-onset depression ($n = 14$); Late-onset bipolar disorder ($n = 14$), & Age- & gender-matched HC for LOS ($n = 21$)	LOS: >44	n/s	LOS = Late-onset depression = Late-onset bipolar disorder LOS: 70.1 Late-onset depression: 69.3 Late-onset bipolar disorder: 73.0	• LOS showed structural and functional differences relative to HC in comparison with late-onset depression and bipolar disorder. • LOS had larger right temporal horns and third ventricles compared with HC; Late-onset depression and bipolar disorder showed more left sylvian fissure, bilateral temporal sulcal enlargement, and bilateral cortical atrophy. • The three patient groups differed only on the degree of right sulcal atrophy (Late-onset depression > Late-onset bipolar disorder > LOS).
	Reeves and Struve (2003), United States	LOS inpatients ($n = 10$)	LOS: 40-59	LOS: ≤ 2	N/A (Onset age: 51.9; current age: 52.8)	• Most LOS showed normal MRI and EEG results (7/10 and 8/10) when compared with age-adjusted normative data.
	Rivkin et al. (2000), United States	LOS ($n = 12$); Elderly EOS ($n = 10$), & Race-, age-, gender-, & hypertension history-matched HC ($n = 31$)	LOS: >50	LOS < EOS LOS: 4.4 EOS: 35.4	LOS = EOS LOS: 71.6 EOS: 64.2	• LOS had insignificantly greater total WMH volumes than EOS and HC. • WMH volume positively correlated with age.
	Wake et al. (2016), Japan	LOS ($n = 19$); HC matched for LOS ($n = 10$), & HC matched for EOS ($n = 27$)	LOS: ≥40	LOS > EOS LOS: 8.2 EOS: 5.3	LOS > EOS LOS: 55.2 EOS: 33.8	• LOS showed hypoperfusion of bilateral temporal lobes (reduced perfusion), while EOS showed hypoperfusion of bilateral prefrontal lobes.

(*continued*)

Table 1. Continued.

Domain	Study, country	Sample	Age of onset cut-off/ range	DOI	Mean age	Main findings
Psychosocial & Psychological	Giblin et al. (2004), United Kingdom	VLOSLP outpatients ($n = 14$); & Very-late onset depression outpatients ($n = 13$); & Age-matched HC ($n = 18$) [a]*authors referred to this group as LOP, but acknowledged the term VLOSLP and used the age of onset cut-off proposed by* Howard et al. (2000)	VLOSLP: >60	VLOSLP = Very-late-onset depression outpatients VLOSLP: 4.33 Very-late-onset depression outpatients: 5.17	LOS = Very-late-onset depression outpatients (matched) LOS: 77.6 Very-late-onset depression outpatients: 76.1	• VLOSLP had more maladaptive schemas compared with HC, but not with very-late-onset depression. • NSD in adverse life events reported in VLOSLP and very-late-onset depression, but both reported more than HC. • Events mainly took place in childhood and related to interpersonal relationships in VLOSLP, and in older-age and related to health-related issues in very-late-onset depression. • VLOSLP had lower morale towards aging and more feelings of loneliness than HC, but no significant differences with very-late-onset depression.
	McCulloch et al. (2006), United Kingdom	VLOSLP[a] ($n = 13$); Late-onset depression ($n = 15$), & Age-matched HC for VLOSLP ($n = 15$) [a]*authors referred to this group as LOP*	VLOSLP: >60	LOP < Late-onset depression VLOSLP: 3.6 Late-onset depression: 18.7	VLOSLP = Late-onset depression VLOSLP: 74.9 Late-onset depression: 77.6	• Overall PWB score was highest in HC, followed by VLOSLP, and lowest in late-onset depression. • HC scored higher than both VLOSLP and in late-onset depression on the Positive Relations with Others domain. • Similar perceived current level of functioning between VLOSLP and HC, except lower Environmental Mastery and Positive Relations with Others for VLOSLP. • VLOSLP showed no perceived change in PWB over time, while HC improved and late-onset depression declined. • No overt depression in VLOSLP and HC; both scored higher on self-esteem than late-onset depression. • Similar response time on Stroop task between VLOSLP and late-onset depression, both longer than HC. • Perceived actual-self score was lower than ideal-self and perceived others' views of self in all 3 groups. • Late-onset depression showed greatest actual-ideal discrepancy and an increase over time compared to VLOSLP and HC. • NSD between groups in actual-other discrepancy (both current and past).

N/A: not available; n/s: not specified; EOP: early-onset psychosis; EOS: early-onset schizophrenia; LOP: late-onset psychosis; LOS: late-onset schizophrenia; VLOSLP: very-late-onset schizophrenia-like psychosis; HC: healthy control; AD: Alzheimer's Disease; ASQ: Attributional Style Questionnaire; BPRS: Brief Psychiatric Rating Scale; CAMCOG: Cambridge Cognition Examination (Section B of the Cambridge Mental Disorders of the Elderly Examination); CPT: Continuous Performance Test; CVLT: California Verbal Learning Test; DOI: Duration of Illness; DRS: Mattis Dementia Rating Scale; DST: Digit Span Test; EEG: Electroencephalography; FA: Fractional Anisotropy; FAB: Frontal Assessment Battery; GAF: Global Assessment of Functioning; HAM-D: Hamilton Rating Scale for Depression; IADL: Instrumental Activities of Daily Living; MD: Mean Diffusivity; MMSE: Mini-Mental State Examination; MRI: Magnetic Resonance Imaging; NPI: Neuropsychiatric Inventory; NSD: No Significant Difference; PANSS: Positive and Negative Syndrome Scale; PDS: Proxy for Deficit Syndrome; PFAQ: Pfeffer's Functional Activities Questionnaire; PRT: Probabilistic Reasoning Task; PWB: Psychological Well-being; RCFT: Rey-Osterrieth Complex Figure Test; TMT: Trail-Making Test; VFT: Verbal Fluency Test; WAIS: Wechsler Adult Intelligence Scale; WAIS-R: WAIS-Revised; WCST: Wisconsin Card Sorting Test; WMH: White Matter Hyperintensity.
[a]All EOS are regarded as EOP and all LOS are regarded as LOP in the text of this review.

illness (DOI) can have statistically significant and clinically relevant impacts on participants' experiences, symptom severity, and outcomes of the condition.

Data extraction and synthesis

Three independent authors (SMYW, YNS, and CLMH) reviewed the titles and abstracts of publications yielded from the systematic search. To increase the reliability of the procedure, the full texts of the studies were then screened independently by two authors (SMYW and YNS) against the inclusion criteria to determine relevance.

Due to considerable heterogeneity in the criteria for LOP and VLOSLP, methods, and outcome measures used in the studies included, a non-statistical narrative approach was adopted to synthesise the findings. Information of each study, including sample and population, participant's characteristics, cut-off age criteria, design and time-points of data collection, outcome measures, and study findings were summarised in Table 1.

Results

Screening and study selection

The initial search resulted in a total of 3085 studies. After cross-checking and duplicates removal by all three authors, 1702 studies remained for potential inclusion. A two-stage screening was then performed to check for the studies' eligibility (first titles and abstracts, then full texts). Twenty-seven studies met the above-stated criteria and were included for data synthesis. A flowchart of the screening process is displayed in Figure 1.

Study characteristics

Types of study samples

Of the 27 included studies, seven included only VLOSLP patients (Barak, Aizenberg, Mirecki, Mazeh, & Achiron, 2002; Giblin, Clare, Livingston, & Howard, 2004; Jones et al., 2005; McCulloch, Clare, Howard, & Peters, 2006; Moore et al., 2006; Reeves, Stewart, & Howard, 2002; Van Assche et al., 2019), one compared VLOSLP with LOP patients (Hanssen et al., 2015), while the remaining examined LOP. All types of psychotic disorders (except those due to dementia or organic disorders) were included in the definition of LOP in this review. The majority of studies on LOP was on psychosis of the SZ type ($n = 15$) (Brichant-Petitjean et al., 2013; Chen et al., 2013; Huang & Zhang, 2009; Laks, Fontenelle, Chalita, & Mendlowicz, 2006; Mason, Stott, & Sweeting, 2013; Rabins, Aylward, Holroyd, & Pearlson, 2000; Reeves & Struve, 2003; Rivkin et al., 2000; Sato, Bottlender, Schröter, & Möller, 2004; Smeets-Janssen et al., 2013; Vahia et al., 2010; Wake et al., 2016; Zakzanis, Andrikopoulos, Young, Campbell, & Sethian, 2003; Zakzanis, Kielar, Young, & Boulos, 2001). This review will use the general terms LOP and VLOSLP to refer to patients with late-onset or very-late-onset SZ. Only one study specifically examined very-late-onset delusional disorder (Harris, Kotsopoulos, & Yamin, 2014).

Age cut-off for LOP and VLOSLP

While Howard's group defined LOP as psychotic symptoms that develop between ages 40 and 60 (Howard et al., 2000), the cut-off for onset age used varied significantly. For instance, the onset age for LOP included 44 (Rabins et al., 2000), 45 (Brichant-Petitjean et al., 2013; Palmer et al., 2003; Zakzanis et al., 2001; 2003), 50 (Brodaty et al., 2003; Girard et al., 2011; Hussein, Shafei, Meguid, Missiry, & Tamara, 2012; Laks et al., 2006; Rivkin et al., 2000), and even 65 (Harris et al., 2014). Late-onset psychosis had also been applied to individuals with first onset at or after age 60 in two studies (Giblin et al., 2004; McCulloch et al., 2006) – which is the criteria for VLOSLP in Howard et al. (2000). As for other studies with VLOSLP samples, five used age 60 as the cut-off (Hanssen et al., 2015; Jones et al., 2005; Moore et al., 2006; Reeves et al., 2002; Van Assche et al., 2019) and one used age 70 (Barak et al., 2002). For the purpose of standardisation in this review, all participants whose first onset were after the age of 40, regardless of their diagnosis, were regarded as 'late-onset' cases and those with onset after age 60 were regarded as 'very-late-onset' cases.

Psychopathological

Psychopathological symptoms of patients with LOP or VLOSLP were studied in ten included studies (Brichant-Petitjean et al., 2013; Brodaty et al., 2003; Hanssen et al., 2015; Huang & Zhang, 2009; Hussein et al., 2012; Mason et al., 2013; Reeves et al., 2002; Sato et al., 2004; Vahia et al., 2010; Wake et al., 2016).

One recent study found no psychopathological differences (based on one assessment scale) between

LOP and EOP (Wake et al., 2016). In partial support of this finding, a previous study that examined patients' symptoms in more detail found no LOP-EOP differences in the proportion with paranoid subtype psychosis and severity of depressive symptoms, LOP patients (including outpatients) presented less overall psychopathology and less severe positive symptoms (Vahia et al., 2010).

The differences of psychopathological profiles between LOP and EOP vary across studies depending on their status as outpatients or inpatients. For outpatients, less severe psychotic symptoms were reported in the LOP when compared with the EOP (Brichant-Petitjean et al., 2013). For inpatients with comparable levels of cognitive and overall functioning and global outcomes, more severe thought disorder symptoms were observed in the LOP than the EOP (Huang & Zhang, 2009). These findings suggested that, comparing with EOP, outpatients with LOP may present fewer and less severe psychotic symptoms, while inpatients present more thought disorder symptoms.

Furthermore, in a group of first-episode, first-admission, and neuroleptic-naïve SZ patients, the LOP presented more systematic persecutory delusion, less affective flattening and social withdrawal than the EOP when adjusted for negative symptoms, duration of hospitalisation, and level of extrapyramidal symptoms (Sato et al., 2004). Mason et al. (2013) reported that a similar proportion of LOP and EOP experienced delusion while hallucination was less frequent and quieter in LOP patients. The LOP with delusions exhibited greater suspiciousness/paranoia, greater belief-conviction, and less insight when adjusted for the chronicity of illness, but not for the chronological age.

While the majority of studies on LOP or VLOSLP excluded those who developed the disorder due to other conditions, one study compared the clinical profiles of LOP with these with late-onset 'other psychoses' (70% had psychosis due to dementia, 20% due to mood disorder, 10% due to a medical condition) to further examine whether and how the psychosis types differ (Hussein et al., 2012). The LOP group showed significantly more positive symptoms and less general psychopathology, particularly more bizarre-type delusions that were complex in nature (e.g. delusions of control, persecution, and passivity). These patients also experienced multi-modal hallucinations, with auditory hallucinations being most prominent and frequent (including running commentary and multiple voices).

The psychopathological symptoms of VLOSLP patients were only examined in two studies (Hanssen et al., 2015; Reeves et al., 2002). The VLOSLP were found to present mainly paranoid symptoms (38%) and persecutory delusions (31%), followed by hallucinations (4%) (Reeves et al., 2002). None of these patients presented thought disorders or negative symptoms, though most patients were considered to have no insight (16 out of 26; 62%). Another study also reported more positive symptoms in the VLOSLP when compared with the EOP group, but not LOP when adjusted for onset age, gender, years of education, and disorganised symptoms (Hanssen et al., 2015).

Neuropsychological

Sixteen of the included studies examined the neuropsychological profiles of LOP and VLOSLP (Brichant-Petitjean et al., 2013; Brodaty et al., 2003; Chen et al., 2013; Girard et al., 2011; Hanssen et al., 2015; Huang & Zhang, 2009; Hussein et al., 2012; Laks et al., 2006; Moore et al., 2006; Palmer et al., 2003; Reeves et al., 2002; Smeets-Janssen et al., 2013; Vahia et al., 2010; Van Assche et al., 2019; Zakzanis et al., 2001; 2003) and one examined very-late-onset delusional disorder (Harris et al., 2014).

Profiles of LOP, VLOSLP, EOP and HC

A longitudinal study on LOP patients found no change in their neurocognitive functions over one year (Laks et al., 2006). Comparing these LOP patients to EOP and HC, three of the included studies found no significant group differences in the extent of cognitive impairment presented (Hanssen et al., 2015; Huang & Zhang, 2009; Palmer et al., 2003). Hanssen et al. (2015), for instance, reported similar levels of general intelligence, memory, attention, and executive functions were found between the LOP and EOP.

Six studies, however, were not in agreement with the above findings and found differences in the areas of cognitive deficits between groups (Brichant-Petitjean et al., 2013; Brodaty et al., 2003; Chen et al., 2013; Girard et al., 2011; Smeets-Janssen et al., 2013; Vahia et al., 2010).

One study found more impairment in executive functions, task switching, attention, immediate recall, and problem-solving in LOP patients than HC (Chen et al., 2013). A longitudinal study that followed-up LOP patients for five years also found significantly more cognitive declines in these patients as compared with HC (Brodaty et al., 2003). It should, however, be

noted that at five-year follow-up, these LOP patients who developed dementia had a mean onset age of 70 ($SD = 13.6$) and those who remained dementia-free had a mean onset age of 67 ($SD = 9.6$), meaning a great proportion of these patients would likely have been VLOSLP patients (i.e. onset above 60).

Meanwhile, comparing with EOP, LOP patients had faster processing speed, better perceptual-organisation abilities, cognitive flexibility, and verbal memory (though only the first two remained significant after adjusting for DOI) (Vahia et al., 2010). Brichant-Petitjean et al. (2013) also found the LOP to have outperformed the EOP on most cognitive measures tested, though their abilities were inferior to those of HC.

Findings were similar concerning the social cognition of LOP patients with paranoid SZ, whose theory of mind abilities were comparable to that of HC and superior to EOP patients, both when adjusting or without adjusting for symptom severity, overall cognitive function, and estimated premorbid intelligence (Smeets-Janssen et al., 2013).

Though the LOP-EOP-HC differences were also reported in Girard et al. (2011), their relationship was less straightforward. Since the two patient groups were not matched on age and education level, standardised scores were calculated for LOP-EOP comparison and their raw scores were individually compared with their respective HC groups (using normative data). The comparison between two patient groups showed comparable overall cognitive functions based on their standardised scores. However, further inspection into the LOP-EOP differences revealed that the EOP exhibited poorer ability to learn or retrieve new information due to interference of prior learning (proactive interference), while LOP showed more executive deficits reflected by more intrusions and poorer cognitive flexibility. Meanwhile, no LOP-HC differences were found after adjusting for age and education level, whereas EOP showed more deficits than matched HC in their episodic memory, semantic fluency, and executive function.

Three of the included studies investigated the cognitive impairments in VLOSLP (Hanssen et al., 2015; Moore et al., 2006; Reeves et al., 2002). Reeves et al. (2002) reported that 23% of the patients (with mean DOI of 3 years) had developed cognitive impairment by the time of study, though there was no data on patients' initial psychopathological or neuropsychological symptoms; data on another population for comparison were also not available for further inspection. Meanwhile, Moore et al. (2006) showed that VLOSLP patients have significantly lower estimated intelligence, poorer working memory, and were less able to attribute correct intentions to others in deception mentalising tasks as compared with HC. Nonetheless, no differences were found between these patients and age- and gender-matched very-late-onset depression patients and HC in their abilities to infer false beliefs from others' actions and perform tasks involving probabilistic reasoning. In the one study that compared VLOSLP and LOP, patients with very-late-onset exhibited poorer attention than LOP when confounding variables were controlled for (Hanssen et al., 2015).

LOP, VLOSLP, EOP, and dementia

In view of the debate on LOP and VLOSLP as prodromes of neurodegenerative diseases, two studies specifically examined the development of dementia in LOP and VLOSLP (Brodaty et al., 2003; Hanssen et al., 2015) and four others compared the cognitive functions of patients with psychosis and HC to those with dementia (Hussein et al., 2012; Palmer et al., 2003; Zakzanis et al., 2001; 2003).

The studies reviewed generally found the neuropsychological profiles of LOP and VLOSLP to be distinguished from dementia. For instance, a longitudinal study found greater cognitive decline in those having Alzheimer's disease (AD) with psychosis in comparison with patients with LOP, EOP, and HC at both one- and two-year follow-up (Palmer et al., 2003). Whereas another study found more cognitive impairments in LOP than the norm, their cognitive function was better than those with psychosis due to dementia (Hussein et al., 2012).

The specific cognitive functions which LOP differ from dementia appear to be influenced by the type of dementia under investigation. Such a view is clearly exemplified in Zakzanis et al. (2001) and Zakzanis et al. (2003) which compared the same group of LOP patients to those with frontotemporal dementia and AD, respectively. The researchers found LOP to be associated with poorer short-term memory, but superior abstract reasoning, mental flexibility, executive control and language skills in comparison with frontotemporal dementia (Zakzanis et al., 2001), while poorer executive control but more intact memory in comparison with AD (Zakzanis et al., 2003).

Brodaty et al. (2003) found significantly more LOP patients (which included VLOSLP patients) have developed dementia at follow-up after five years as compared with HC (nine of 19 LOP patients versus none of 24 HC). Nonetheless, other studies have only

shown partial support to the view that the cognitive deficits in VLOSLP resemble those in dementia patients. For instance, VLOSLP patients and those having AD with psychosis and Lewy Body Dementia showed comparable levels of processing speed, working memory, attention, executive functions, and perceptual abilities (Van Assche et al., 2019). However, these VLOSLP patients also exhibited better consolidation functions than those having AD with psychosis and better learning abilities, language, and visuo-construction skills than both dementia groups. Additionally, although four of 32 VLOSLP patients displayed early signs of probable dementia at one-year follow-up (versus none in LOP, EOP, or HC groups) in Hanssen et al. (2015), the cognitive functions of VLOSLP patients (excluding those four with probable dementia) were not found to differ from EOP and LOP. Only when possible confounding variables were controlled for that the VLOSLP patients showed poorer attention than LOP patients.

While the studies above either found better cognitive functions in LOP and VLOSLP than dementia or similar abilities in VLOSLP and dementia, more impairments in some cognitive processes had been reported in very-late-onset delusional disorder when compared with AD patients (Harris et al., 2014). Apart from better episodic memory and normal immediate recall in both groups, those with very-late-onset delusional disorder had significantly poorer abilities in conceptual reasoning, object recognition, processing speed, naming, divided attention, working memory, and visuo-perceptual planning and organisation.

Neurobiological

Five of the included studies examined the neurobiology of LOP (Chen et al., 2013; Rabins et al., 2000; Reeves & Struve, 2003; Rivkin et al., 2000; Wake et al., 2016) and two other studies focused on VLOSLP (Barak et al., 2002; Jones et al., 2005). All these studies compared LOP or VLOSLP patients to age-matched participants which minimised the effect of structural changes resulting from aging. The findings were mixed: four found neurobiological differences between LOP or VLOSLP and other conditions (Barak et al., 2002; Chen et al., 2013; Rabins et al., 2000; Wake et al., 2016), while the other three found otherwise (Jones et al., 2005; Reeves & Struve, 2003; Rivkin et al., 2000).

Data from electroencephalogram (EEG) in a study (Reeves & Struve, 2003) revealed there were no significant differences between LOP and the norm (age-adjusted normative values). In contrast, data from diffusion tensor imaging (DTI) showed significantly more fractional anisotropy (FA) reductions in the left parietal lobe and right posterior cingulum of the LOP in comparison with age-, gender-, and education-matched HC (Chen et al., 2013). No association, however, was found between FA values and severity of psychotic symptoms.

With regard to the inconsistencies in findings pertaining to the volume of white matter hyperintensities (WMH) in LOP and EOP, Rivkin et al. (2000) posited a reason may be due to mismatch in the measurement choice (i.e. using ordinal methods as in previous studies to measure a continuous variable, such as WMH volume). Hence in their MRI study, the researchers compared the total WMH volumes of LOP, age-, race- and gender-ratio-matched EOP, and HC without sub-dividing the volume by region. While no significant group differences were found, the WMH volume was found to be positively correlated with age. The total WMH volume of LOP patients was also nearly five and ten times greater than the HC and EOP, respectively.

In addition to EOP, one study compared the MRI findings of LOP to age-, gender- and handedness-matched late-onset depression and bipolar disorder patients and HC (Rabins et al., 2000). The findings showed the LOP had the least degree of right sulcal atrophy in comparison with the mood disorder groups but enlarged right temporal horns and third ventricles when compared with HC.

More recently, a study using single-photon emission computed tomography found regional cerebral blood flow (rCBF) abnormalities in both EOP and LOP patients though in different manners. The LOP group mainly presented hypoperfusion in the bilateral temporal lobes, while EOP had hypoperfusion in the bilateral prefrontal lobes (Wake et al., 2016). No group differences were found in patients' severity of psychotic symptoms and estimated intelligence quotient (IQ), meaning these variables may not explain the rCBF abnormalities in LOP and EOP.

As for VLOSLP, some researchers previously found their FA and mean diffusivity measures to be not different from HC (using DTI) on the uncinate, superior longitudinal fasciculus, inferior occipitofrontal fasciculi, and the cingulum (Jones et al., 2005). They thus argued that psychosis with a 'very late onset' cannot be attributed to focal white-matter pathology within these fibre tracts which some had raised. In comparison with long-stay EOS inpatients, computed

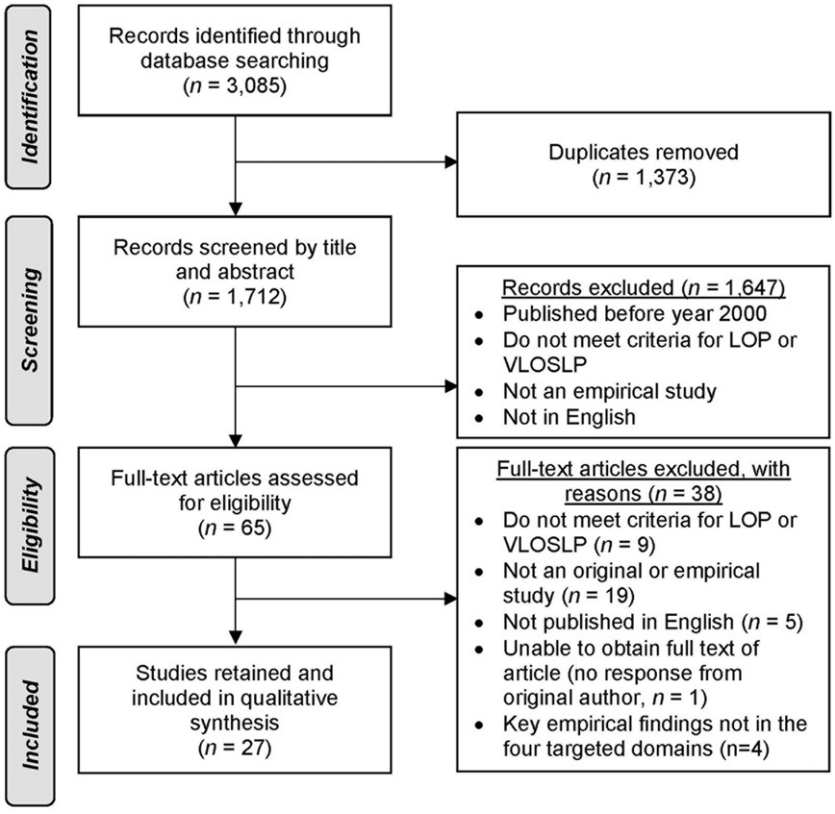

Figure 1. PRISMA flow diagram of the study selection process.

tomography scans showed that VLOSLP patients had a greater cerebellar ventral-to-brain ratio (VBR; i.e. more significant cerebellar atrophy) but with no differences in their VBR of the frontal horn, levels of cortical atrophy, or periventricular white matter leukoencephalopathy (Barak et al., 2002).

Psychosocial and psychological

Only one study investigated the psychosocial correlates and outcomes of VLOSLP (Giblin et al., 2004), and another examined the psychological processes underlying VLOSLP (McCulloch et al., 2006) in comparison with late- or very-late-onset depression and HC.

Giblin et al. (2004) reported more adverse life events in VLOSLP than HC but not in those with very-late-onset depression. Both patient groups reported experiencing similar levels of loss in response to adverse life events, though the events were mainly in childhood for VLOSLP and older-age for very-late-onset depression. Proportionally more VLOSLP patients reported experiences of discriminating-threatening events or fragile relationships, while health-related difficulties were more frequently experienced by depressive patients. Although the patient groups did not differ in their levels of overall maladaptive schemas, those with VLOSLP presented more schemas in the domains of other-directedness (e.g. self-sacrifice) and over-vigilance and inhibition (e.g. unrelenting standards). Compared with the HC, VLOSLP patients showed lower overall morale regarding aging and more feelings of loneliness and life dissatisfaction that were not different from depressive patients.

In McCulloch et al. (2006), the level of psychological well-being in VLOSLP was lower than the HC but higher than that of patients with late-onset depression (which included very-late-onset patients). Similarly, no perceived change in psychological well-being was reported in VLOSLP, whereas more improvements and declines were seen in HC and late-onset depression, respectively. One dimension of psychological well-being that differed between groups, however, concerns Positive Relations with Others, where HC scored significantly higher than both patient groups. Similar to the HC, VLOSLP patients did not exhibit overt depression and had higher self-esteem than those with late-onset depression. Yet, both patient groups showed more covert negative self-evaluations (demonstrated by a slower response

in the emotional Stroop task). Such findings suggest VLOSLP may be characterised by covert but not overt depression.

Discussion

Of the 27 identified studies, the majority compared the clinical presentation of LOP and VLOSLP with EOP and HC; other conditions which LOP and VLOSLP had been compared with included dementia, depression, and bipolar disorder. These studies provided some evidence to answer the questions on how and to what extent LOP and VLOSLP are similar to or different from the typical early adulthood-onset psychosis, the healthy population, neurodegenerative diseases, and affective disorders.

Overall, findings for both LOP and VLOSLP across the four domains lacked consistency and were sometimes contradicting. Some reasons may be attributable to the (i) lack of standardisation in the cut-off age and terminology used for LOP and VLOSLP, (ii) small sample size, and (iii) lack of consideration for confounding variables, such as current age, illness chronicity, and inpatient/outpatient status in most studies. The scarcity of studies on LOP and VLOSLP also make findings difficult to generalise and offer conclusive remarks.

Criteria for LOP and VLOSLP

Despite the publication of the international consensus statement on LOP and VLOSLP nearly two decades ago (Howard et al., 2000), the current review – which included only studies published thereafter – revealed much misalignment still exists in the diagnostic terminologies and criteria used. While the majority of studies with VLOSLP samples used the recommended onset age of 60 years as the cut-off, nearly half of the studies on LOP did not adopt the onset age criterion of 40–60 years. Furthermore, the majority of LOP studies did not draw an upper onset age limit (see Table 1), meaning VLOSLP patients had likely been mixed with LOP in at least some studies.

Some researchers reasoned that, since no significant differences were found between LOP and VLOSLP in a previous study (Girard & Simard, 2008), a different cut-off age (50 years or above) had been chosen to improve recruitment strategy (Girard et al., 2011). The mixing of LOP and VLOSLP as such or referring to those with onset after age 60 as LOP (e.g. Giblin et al., 2004; McCulloch et al., 2006) makes comparing the condition difficult and confusing, especially in the current field where much less is known about the late-onset conditions. Previous reviews had also noted that inappropriate choices of definition and criteria could lead these late-onset conditions to be overlooked or misdiagnosed, which may contribute to the conflicting findings across studies (Jeste, Blazer, & First, 2005; Pearman & Batra, 2012). An exception for different cut-offs for delusional disorder may nonetheless be allowed as the condition generally have a later onset than SZ (including paranoid SZ) and other psychotic disorders (Marneros, Pillmann, & Wustmann, 2012; Muñoz-Negro et al., 2018; Suvisaari et al., 2009).

Small sample size

As can be seen in Table 1, the sample size of the included studies is generally small. It is, therefore, possible that true effects may have been undetected and statistically significant results may instead be false-positive findings. A reason for the small sample sizes concerns the relatively lower prevalence of LOP and VLOSLP in the population. Several studies have reported difficulties in recruiting LOP and VLOSLP patients due to the low number of clinical cases or difficulties in recruiting community-dwelling cases and retaining them in follow-up or longitudinal studies (e.g. Barak et al., 2002; Howard et al., 2018). Whether the low prevalence is truly due to lower chances of developing psychotic disorders after the age of 40, or rather, failure to recognise symptoms as LOP or VLOSLP and lower motivation of clinicians to give such diagnoses as opposed to neurodegenerative diseases necessitates further investigation.

Inconsistent findings with the current literature

Psychopathological

The findings of psychopathological profiles of VLOSLP were in agreement with previous studies (Howard et al., 2000; Sharma, Debsikdar, Naphade, & Shetty, 2014) while those of LOP were rather inconsistent. Findings that more paranoid SZ, persecutory delusion, and suspiciousness but less severe overall psychotic symptoms comparing with EOP were in line with the evidence in the literature (Howard, Castle, Wessely, & Murray, 1993; Roche, Creed, MacMahon, Brennan, & Clarke, 2015). One study, however, found no major differences but more thought disorder symptoms in LOP comparing with elderly EOP inpatients (Huang & Zhang, 2009). The inconsistent findings on the differences in patients'

psychopathological profiles may be associated with the differences in illness chronicity, which revealed to be a significant factor affecting symptom presentation in LOP and EOP and which is positively associated with thought disorder symptoms (Maeda et al., 2007; Mason et al., 2013).

Neuropsychological

The LOP and VLOSLP were generally found to present more deficits in the neuropsychological profiles when compared with HC and EOP, though the overall cognitive function was generally better than EOP. One study, on the other hand, found no differences in cognitive abilities between LOP, EOP, and HC over a two-year period, whereas psychosis with dementia and cognitive impairment showed significantly greater decline comparatively (Palmer et al., 2003). This finding should, however, be noted that only two instruments typically used to assess cognitive functions for detecting dementia and mild cognitive impairments (i.e. Mini-Mental State Exam and Dementia Rating Scale) were used. The measures are rather more global than other more comprehensive neuropsychological batteries (e.g. the Wechsler Adult Intelligence Scale). The use of instruments which have lower validity to measure cognitive ability (Rajji & Mulsant, 2008) may have led to the lack of sensitivity to detect the differences between groups. Yet, the findings lend support to the view that LOP is not a neurodegenerative condition (Palmer et al., 2003). Like LOP, the areas which cognitive impairments were seen in VLOSLP and very-late onset delusional disorder differ from different types of dementia studied (Harris et al., 2014; Van Assche et al., 2019; Zakzanis et al., 2001; 2003), which provide some evidence suggesting that VLOSLP is not necessarily a prodrome of dementia. Considering the debate on whether VLOSLP constitutes a sub-type of psychotic or neurodegenerative disorder remains, this would be an important direction for future research.

Neurobiological

Both LOP and VLOSLP generally show altered brain structures and activities as compared with HC, though findings solely based on studies reviewed in this paper are inconclusive. For instance, Reeves and Struve (2003) found no EEG differences between LOP patients and the age-adjusted mean values derived from a normative database (John, Prichep, Fridman, & Easton, 1988). The use of age-matched normative data for comparison, instead of HC matched on variables not limited to age (e.g. education level, gender) and who had undergone similar assessment procedures, provided less room for further investigation. Furthermore, although chronic EOP patients had previously been found to differ from HC in their EEG amplitudes, such differences were not replicated in first-episode patients and those with at-risk mental state (Ranlund et al., 2014). The finding of Reeves and Struve (2003) may thus have also been influenced by patients' relatively short DOI (i.e. two years or less). Since previous studies had not shown EEG abnormalities to be a consistent biomarker of psychosis (Boutros et al., 2008; Manchanda, Malla, Harricharan, Cortese, & Takhar, 2003), more rigorously designed studies are needed to testify the speculation.

Rivkin et al. (2000) should be commended for pointing out the impact of choice of study design and measurement methods on study outcomes. The researchers raised concerns over the use of ordinal measures to examine continuous variables like WMH volume and hence chose to compare the total WMH volume between LOP, EOP, and HC as a continuous variable. However, the negligence of potential regional WMH volume differences between groups and only considering the total WMH volume makes the analysis insensitive to local abnormalities. The trend of greater WMH total volume in LOP compared with EOP and HC suggest regional differences in WMH volume may exist between groups. Further explorations in this area may provide further information that help to fill gaps about the late-onset condition in the literature.

Psychosocial and psychological

Unexpectedly, only two studies examined the psychosocial and psychological characteristics of VLOSLP and neither compared the group with LOP or EOP, but with HC and late- and very-late onset depression. Consistent with studies suggesting the relationship between significant life events and mental disorders, including psychosis (Bramon & Murray, 2001; Varese et al., 2012), both VLOSLP and very-late onset depression reported more adverse life events and losses than HC (Giblin et al., 2004). Even when the VLOSLP reported better perceived well-being comparing with late- and very-late-onset depression (McCulloch et al., 2006), the one dimension which the groups did not differ is Positive Relations with Others, suggesting that perceived inadequate interpersonal relationship could be a significant stressor in

VLOSLP that may at least partially contribute to the development of the condition.

Current and future directions

The current review provides a preliminary understanding of the clinical presentation of LOP and VLOSLP. With focus on studies after year 2000 (i.e. publication of the international consensus by Howard et al., 2000) in this review, it was expected that terminologies and definitions would be more aligned across studies. This was, unfortunately, not the case as reflected by the numerous cut-off points used for onset age and the mixing of LOP and VLOSLP samples in the reviewed studies. It was not the authors' intention to discount or discredit any studies published before then. Consideration of earlier findings may well assist in the construction of a more coherent picture of LOP and VLOSLP and how they relate to other conditions. Extension of study inclusion criteria to years before 2000 could be a direction for future research.

In consideration of the limitations in existing studies as mentioned earlier, it is important for future research in LOP and VLOSLP to i) specify the onset age criteria for the conditions (including upper age limit, if any); ii) study LOP and VLOSLP separately instead of combined; iii) expand sites for recruitment (e.g. via collaboration with other centres or researchers) to increase sample size when possible, and iv) account for different confounding variables (e.g. other psychiatric and physical symptoms, DOI and illness chronicity, length of hospital stay if inpatient, type and dosage of medication, sociodemographic and environmental factors). More longitudinal studies with longer follow-up periods would also be critical to determine the prognoses of LOP and VLOSLP and reflect whether the conditions are better viewed as static encephalopathies or neurodegenerative conditions (Van Assche et al., 2017).

After all, the aim of the current review is not to argue for LOP and VLOSLP to be regarded as entirely separate constructs from EOP and other conditions. The use of 'early-onset', 'late-onset', and 'very-late-onset' labels to distinguish between conditions was hoped to assist researchers to further explore differences in their underlying mechanisms. The labels may indeed be discarded when there is solid evidence to suggest lack of differentiation between the conditions. Other cut-off points to define 'late-onset' may also be adopted, especially for specific psychotic disorders (such as delusional disorder) given their mean onset age are different. However, only with clear supporting evidence from multiple testing and rigorously designed studies should the existing labels and cut-offs be replaced to avoid further misalignments in terminologies across studies. Since differences in aetiologies and outcomes had been observed across EOP, LOP and VLOSLP, researchers are suggested to adopt the criteria proposed by Howard et al. (2000) for comparison of findings across studies. This would allow for a more precise understanding of the conditions that is crucial for early detection as well as the development of effective preventive intervention and treatment targeted at these individuals.

Apart from studies on the risk factors and clinical presentation of LOP and VLOSLP, future research may place greater emphasis on the possible treatment approaches for these patients. For instance, pharmacological treatment has long been viewed as the key treatment option for persons with SZ and other psychotic disorders (Kane & Correll, 2010; Patel, Cherian, Gohil, & Atkinson, 2014). However, treatment for LOP or VLOSLP may be somewhat different from that for EOP as older adults tend to experience more severe and frequent extrapyramidal side effects from pharmacotherapy (Iglewicz, Meeks, & Jeste, 2011). Previous studies had also reported low treatment retention rates and high number of lost cases at follow-up in these patients (e.g. (Lam, Reeves, Stewart, & Howard, 2016) which may make medication discontinuance a greater problem. A comprehensive evaluation of the risks and benefits of pharmacological treatment as suggested by some researchers (e.g. Chan, Lam, & Chen, 2011) is therefore crucial.

After all, the current review is not arguing for LOP and VLOSLP to be viewed as conditions entirely distinct from EOP or other conditions. Rather, it is hoped that a better understanding of the conditions can be developed to allow for earlier detection, prevention, and intervention. The 'late-onset' labels may be unneeded in the future when solid evidence exists to suggest lack of differentiation between late-onset and early-onset psychosis. Other cut-off points to define 'late-onset' may also be proposed for specific psychotic disorders given their differences in average onset age (e.g. delusional disorder); however, only with clear supporting evidence after rigorous testing and consensus among researchers achieved should the original cut-off be fully replaced.

To conclude, while the literature on psychotic disorders has predominately focused on the early- or typical-onset type, findings in this review evidently

point towards the need for the late-onset conditions to be further investigated. It is hoped the current systematic review can provide a basis for future research.

Disclosure statement

EYHC has received speaker honoraria from Otsuka and DSK BioPharma, research funding from Otsuka, and participated in paid advisory boards for Jansen and DSK BioPharma; EYHC reports no other relationship or activity that appear to have influenced the submitted work. The remaining authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper. The authors received no specific funding for this work.

ORCID

Y. N. Suen http://orcid.org/0000-0003-2766-8476
Christy L. M. Hui http://orcid.org/0000-0001-6912-208X
Sherry K. W. Chan http://orcid.org/0000-0003-2712-5826
Edwin H. M. Lee http://orcid.org/0000-0002-8909-0676
Wing C. Chang http://orcid.org/0000-0002-3581-8895
Eric Y. H. Chen http://orcid.org/0000-0002-5247-3593

References

American Psychiatric Association. (1980). *DSM-III: Diagnostic and statistical manual of mental disorder* (3rd ed.). Washington, DC: The Association.

American Psychiatric Association. (1987). *DSM-III-R: Diagnostic and statistical manual of mental disorder* (3rd revised ed.). Washington, DC: The Association.

American Psychiatric Association. (1994). *Mini DSM-IV TR: Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: The Association.

Barak, Y., Aizenberg, D., Mirecki, I., Mazeh, D., & Achiron, A. (2002). Very late-onset schizophrenia-like psychosis: Clinical and imaging characteristics in comparison with elderly patients with schizophrenia. *The Journal of Nervous and Mental Disease*, *190*(11), 733–736. doi:10.1097/01.NMD.0000038167.15155.D6

Beddington, J., Cooper, C. L., Field, J., Goswami, U., Huppert, F. A., Jenkins, R., … Thomas, S. M. (2008). The mental wealth of nations. *Nature*, *455*(7216), 1057–1060. doi:10.1038/4551057a

Bleuler, M. (1943). Die spatschizophrenen Krankheitsbilder. *Fortschritte Der Neurologie Und Psychiatrie*, *15*, 259–290.

Boutros, N. N., Arfken, C., Galderisi, S., Warrick, J., Pratt, G., & Iacono, W. (2008). The status of spectral EEG abnormality as a diagnostic test for schizophrenia. *Schizophrenia Research*, *99*(1–3), 225–237. doi:10.1016/j.schres.2007.11.020

Bramon, E., & Murray, R. M. (2001). A plausible model of schizophrenia must incorporate psychological and social, as well as neuro developmental, risk factors. *Dialogues Clin Neurosci*, *3*(4), 243–256.

Brichant-Petitjean, C., Legauffre, C., Ramoz, N., Ades, J., Gorwood, P., & Dubertret, C. (2013). Memory deficits in late-onset schizophrenia. *Schizophrenia Research*, *151*(1–3), 85–90. doi:10.1016/j.schres.2013.08.021

Brodaty, H., Sachdev, P., Koschera, A., Monk, D., & Cullen, B. (2003). Long-term outcome of late-onset schizophrenia: 5-year follow-up study. *The British Journal of Psychiatry: The Journal of Mental Science*, *183*, 213–219. doi:10.1192/bjp.183.3.213

Brunelle, S., Cole, M. G., & Elie, M. (2012). Risk factors for the late-onset psychoses: A systematic review of cohort studies. *International Journal of Geriatric Psychiatry*, *27*(3), 240–252. doi:10.1002/gps.2702

Chan, W. C., Lam, L. C., & Chen, E. Y. (2011). Recent advances in pharmacological treatment of psychosis in late life. *Current Opinion in Psychiatry*, *24*(6), 455–460. doi:10.1097/YCO.0b013e32834a3f47

Chen, L., Chen, X., Liu, W., Wang, Q., Jiang, T., Wang, J., … Tang, J. (2013). White matter microstructural abnormalities in patients with late-onset schizophrenia identified by a voxel-based diffusion tensor imaging. *Psychiatry Research: Neuroimaging*, *212*(3), 201–207. doi:10.1016/j.pscychresns.2012.05.009

Chen, L., Selvendra, A., Stewart, A., & Castle, D. (2018). Risk factors in early and late onset schizophrenia. *Comprehensive Psychiatry*, *80*, 155–162. doi:10.1016/j.comppsych.2017.09.009

Cohen, C. I. (2018). Very late-onset schizophrenia-like psychosis: Positive findings but questions remain unanswered. *The Lancet Psychiatry*, *5*(7), 528–529. doi:10.1016/S2215-0366(18)30174-3

Essali, A., & Ali, G. (2012). Antipsychotic drug treatment for elderly people with late-onset schizophrenia. *Cochrane Database Syst Rev*, *15*(2), CD004162. doi:10.1002/14651858.CD004162.pub2

Giblin, S., Clare, L., Livingston, G., & Howard, R. (2004). Psychosocial correlates of late-onset psychosis: Life experiences, cognitive schemas, and attitudes to ageing. *International Journal of Geriatric Psychiatry*, *19*(7), 611–623. doi:10.1002/gps.1129

Girard, C., & Simard, M. (2008). Clinical characterization of late-and very late-onset first psychotic episode in psychiatric inpatients. *The American Journal of Geriatric Psychiatry*, *16*(6), 478–487. doi:10.1097/JGP.0b013e31816c7b3c

Girard, C., Simard, M., Noiseux, R., Laplante, L., Dugas, M., Rousseau, F., … Bernier, P. J. (2011). Late-onset-psychosis: Cognition. *International Psychogeriatrics*, *23*(8), 1301–1316. doi:10.1017/S1041610211000238

Hanssen, M., van der Werf, M., Verkaaik, M., Arts, B., Myin-Germeys, I., van Os, J., … Köhler, S, Genetic Risk and Outcome in Psychosis study group (2015). Comparative study of clinical and neuropsychological characteristics between early-, late and very-late-onset schizophrenia-spectrum disorders. *The American Journal of Geriatric Psychiatry*, *23*(8), 852–862. doi:10.1016/j.jagp.2014.10.007

Harris, B. S., Kotsopoulos, E. J., & Yamin, S. (2014). Phenotypic cognitive impairment in late-onset delusional disorder. *International Psychogeriatrics*, *26*(6), 965–975. doi:10.1017/S1041610214000106

Howard, R., Castle, D., Wessely, S., & Murray, R. (1993). A comparative study of 470 cases of early-onset and late-onset schizophrenia. *British Journal of Psychiatry*, *163*(3), 352–357. doi:10.1192/bjp.163.3.352

Howard, R., Cort, E., Bradley, R., Harper, E., Kelly, L., Bentham, P., … Gray, R. (2018). Amisulpride for very late-onset schizophrenia-like psychosis: The ATLAS three-arm RCT. *Health Technology Assessment*, *22*(67), 1–62. doi:10.3310/hta22670

Howard, R. J., Graham, C., Sham, P., Dennehey, J., Castle, D. J., Levy, R., & Murray, R. (1997). A controlled family study of late-onset non-affective psychosis (late paraphrenia). *British Journal of Psychiatry*, *170*(6), 511–514. doi:10.1192/bjp.170.6.511

Howard, R., Rabins, P. V., Seeman, M. V., & Jeste, D. V. (2000). Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: An international consensus. *American Journal of Psychiatry*, *157*(2), 172–178. doi:10.1176/appi.ajp.157.2.172

Huang, C., & Zhang, Y. L. (2009). Clinical differences between late-onset and early-onset chronically hospitalized elderly schizophrenic patients in Taiwan. *International Journal of Geriatric Psychiatry*, *24*(10), 1166–1172. doi:10.1002/gps.2241

Hussein, H., Shafei, A. E., Meguid, M. A. E., Missiry, M. E., & Tamara, M. (2012). Studying late-onset schizophrenia and non schizophrenia psychosis in elderly Egyptian patients. *Middle East Current Psychiatry*, *19*(1), 12–22. doi:10.1097/01.XME.0000407866.00571.95

Iglewicz, A., Meeks, T. W., & Jeste, D. V. (2011). New wine in old bottle: Late-life psychosis. *Psychiatric Clinics of North America*, *34*(2), 295–318. vii. doi:10.1016/j.psc.2011.02.008

Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, *468*(7321), 187–193. doi:10.1038/nature09552

Jeste, D. V. (1993). Late-life schizophrenia: Editor's introduction. *Schizophrenia Bulletin*, *19*(4), 687–689. doi:10.1093/schbul/19.4.687

Jeste, D. V., Blazer, D. G., & First, M. (2005). Aging-related diagnostic variations: Need for diagnostic criteria appropriate for elderly psychiatric patients. *Biological Psychiatry*, *58*(4), 265–271. doi:10.1016/j.biopsych.2005.02.004

John, E. R., Prichep, L. S., Fridman, J., & Easton, P. (1988). Neurometrics: Computer-assisted differential diagnosis of brain dysfunctions. *Science*, *239*(4836), 162–169. doi:10.1126/science.3336779

Jones, D. K., Catani, M., Pierpaoli, C., Reeves, S. J., Shergill, S. S., O'sullivan, M., … Howard, R. J. (2005). A diffusion tensor magnetic resonance imaging study of frontal cortex connections in very-late-onset schizophrenia-like psychosis. *American Journal of Geriatric Psychiatry*, *13*(12), 1092–1099. doi:10.1176/appi.ajgp.13.12.1092

Jordan, G., MacDonald, K., Pope, M. A., Schorr, E., Malla, A. K., & Iyer, S. N. (2018). Positive changes experienced after a first episode of psychosis: A systematic review. *Psychiatric Services*, *69*(1), 84–99. doi:10.1176/appi.ps.201600586

Kane, J. M., & Correll, C. U. (2010). Past and present progress in the pharmacologic treatment of schizophrenia. *The Journal of Clinical Psychiatry*, *71*(09), 1115–1124. doi:10.4088/JCP.10r06264yel

Kwak, Y. T., Yang, Y. S., & Koo, M. S. (2015). Late-Onset psychosis; is it real? *Dementia and Neurocognitive Disorders*, *12*(1), 1–11. doi:10.12779/dnd.2015.14.1.1

Laks, J., Fontenelle, L. F., Chalita, A., & Mendlowicz, M. V. (2006). Absence of dementia in late-onset schizophrenia: A one year follow-up of a Brazilian case series. *Arquivos de Neuro-Psiquiatria*, *64*(4), 946–949. doi:10.1590/s0004-282x2006000600011

Lam, C. C. S. F., Reeves, S. J., Stewart, R., & Howard, R. (2016). Service and treatment engagement of people with very late-onset schizophrenia-like psychosis. *BJPsych Bulletin*, *40*(4), 185–186. doi:10.1192/pb.bp.115.051599

Maeda, K., Kasai, K., Uetsuki, M., Hata, A., Araki, T., Rogers, M. A., … Iwanami, A. (2007). Increased positive thought disorder with illness duration in patients with schizophrenia. *Psychiatry and Clinical Neurosciences*, *61*(6), 687–690. doi:10.1111/j.1440-1819.2007.01730.x

Maglione, J. E., Thomas, S. E., & Jeste, D. V. (2014). Late-onset schizophrenia: Do recent studies support categorizing LOS as a subtype of schizophrenia? *Current Opinion in Psychiatry*, *27*(3), 173–178. doi:10.1097/YCO.0000000000000049

Manchanda, R., Malla, A., Harricharan, R., Cortese, L., & Takhar, J. (2003). EEG abnormalities and outcome in first-episode psychosis. *The Canadian Journal of Psychiatry*, *48*(11), 722–726. doi:10.1177/070674370304801103

Marneros, A., Pillmann, F., & Wustmann, T. (2012). Delusional disorders–are they simply paranoid schizophrenia? *Schizophrenia Bulletin*, *38*(3), 561–568. doi:10.1093/schbul/sbq125

Mason, O., Stott, J., & Sweeting, R. (2013). Dimensions of positive symptoms in late versus early onset psychosis. *International Psychogeriatrics*, *25*(2), 320–327. doi:10.1017/S1041610212001731

McCulloch, Y., Clare, L., Howard, R., & Peters, E. (2006). Psychological processes underlying delusional thinking in late-onset psychosis: A preliminary investigation. *International Journal of Geriatric Psychiatry*, *21*(8), 768–777. doi:10.1002/gps.1561

Meesters, P. D., de Haan, L., Comijs, H. C., Stek, M. L., Smeets-Janssen, M. M. J., Weeda, M. R., … Beekman, A. T. F. (2012). Schizophrenia spectrum disorders in later life: Prevalence and distribution of age at onset and sex in a Dutch catchment area. *The American Journal of Geriatric Psychiatry*, *20*(1), 18–28. doi:10.1097/JGP.0b013e3182011b7f

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., … Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*, *4*(1), 1. doi:10.1186/2046-4053-4-1

Moore, R., Blackwood, N., Corcoran, R., Rowse, G., Kinderman, P., Bentall, R., & Howard, R. (2006). Misunderstanding the intentions of others: An exploratory study of the cognitive etiology of persecutory delusions in very late-onset schizophrenia-like psychosis. *The American Journal of Geriatric Psychiatry*, *14*(5), 410–418. doi:10.1097/01.JGP.0000200604.47367.38

Muñoz-Negro, J. E., Ibáñez-Casas, I., de Portugal, E., Lozano-Gutiérrez, V., Martínez-Leal, R., & Cervilla, J. A. (2018). A psychopathological comparison between delusional disorder and schizophrenia. *The Canadian Journal of Psychiatry*, *63*(1), 12–19. doi:10.1177/0706743717706347

Palmer, B. W., Bondi, M. W., Twamley, E. W., Thal, L., Golshan, S., & Jeste, D. V. (2003). Are late-onset schizophrenia spectrum disorders neurodegenerative conditions? Annual rates of change on two dementia measures. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *15*(1), 45–52. doi:10.1176/jnp.15.1.45

Patel, K. R., Cherian, J., Gohil, K., & Atkinson, D. (2014). Schizophrenia: Overview and treatment options. *P & T: A Peer-Reviewed Journal for Formulary Management*, *39*(9), 638–645.

Pearman, A., & Batra, A. (2012). Late-Onset schizophrenia: A review for clinicians. *Clinical Gerontologist*, *35*(2), 126–147. doi:10.1080/07317115.2011.642943

Rabins, P. V., Aylward, E., Holroyd, S., & Pearlson, G. (2000). MRI findings differentiate between late-onset schizophrenia and late-life mood disorder. *International Journal of Geriatric Psychiatry*, *15*(10), 954–960. doi:10.1002/1099-1166(200010)15:10 < 954::aid-gps224 > 3.0.co;2-o

Rajji, T. K., & Mulsant, B. H. (2008). Nature and course of cognitive function in late-life schizophrenia: A systematic review. *Schizophrenia Research*, *102*(1–3), 122–140. doi:10.1016/j.schres.2008.03.015

Ranlund, S., Nottage, J., Shaikh, M., Dutt, A., Constante, M., Walshe, M., … Bramon, E. (2014). Resting EEG in psychosis and at-risk populations–a possible endophenotype? *Schizophrenia Research*, *153*(1–3), 96–102. doi:10.1016/j.schres.2013.12.017

Reeves, S., Stewart, R., & Howard, R. (2002). Service contact and psychopathology in very-late-onset schizophrenia-like psychosis: The effects of gender and ethnicity. *International Journal of Geriatric Psychiatry*, *17*(5), 473–479. doi:10.1002/gps.614

Reeves, R. R., & Struve, F. A. (2003). Quantitative electroencephalography in late-onset schizophrenia. *International Psychogeriatrics*, *15*(3), 273–278. doi:10.1017/S1041610203009529

Rivkin, P., Kraut, M., Barta, P., Anthony, J., Arria, A. M., & Pearlson, C. (2000). White matter hyperintensity volume in late-onset and early-onset schizophrenia. *International Journal of Geriatric Psychiatry*, *15*(12), 1085–1089. doi:10.1002/1099-1166(200012)15:12. <1085::aid-gps250 > 3.0.co;2-x

Roche, E., Creed, L., MacMahon, D., Brennan, D., & Clarke, M. (2015). The epidemiology and associated phenomenology of formal thought disorder: A systematic review. *Schizophrenia Bulletin*, *41*(4), 951–962. doi:10.1093/schbul/sbu129

Rossler, W., Salize, H. J., van Os, J., & Riecher-Rossler, A. (2005). Size of burden of schizophrenia and psychotic disorders. *European Neuropsychopharmacology*, *15*(4), 399–409. doi:10.1016/j.euroneuro.2005.04.009

Sachdev, P. S., Mohan, A., Taylor, L., & Jeste, D. V. (2015). DSM-5 and mental disorders in older individuals: An overview. *Harvard Review of Psychiatry*, *23*(5), 320–328. doi:10.1097/HRP.0000000000000090

Sato, T., Bottlender, R., Schröter, A., & Möller, H.-J. (2004). Psychopathology of early-onset versus late-onset schizophrenia revisited: An observation of 473 neuroleptic-naive patients before and after first-admission treatments. *Schizophrenia Research*, *67*(2–3), 175–183. doi:10.1016/S0920-9964(03)00015-X

Sharma, E. R., Debsikdar, A. V., Naphade, N. M., & Shetty, J. V. (2014). Very Late-onset Schizophrenia Like Psychosis: Case series and future directions. *Indian Journal of Psychological Medicine*, *36*(2), 208–210. doi:10.4103/0253-7176.130999

Smeets-Janssen, M. M., Meesters, P. D., Comijs, H. C., Eikelenboom, P., Smit, J. H., de Haan, L., … Stek, M. L. (2013). Theory of Mind differences in older patients with early-onset and late-onset paranoid schizophrenia. *International Journal of Geriatric Psychiatry*, *28*(11), 1141–1146. doi:10.1002/gps.3933

Stafford, J., Howard, R., & Kirkbride, J. B. (2018). The incidence of very late-onset psychotic disorders: A systematic review and meta-analysis, 1960-2016. *Psychological Medicine*, *48*(11), 1775–1786. doi:10.1017/S0033291717003452

Suvisaari, J., Aalto-Setälä, T., Tuulio-Henriksson, A., Härkänen, T., Saarni, S. I., Perälä, J., … Lönnqvist, J. (2009). Mental disorders in young adulthood. *Psychological Medicine*, *39*(2), 287–299. doi:10.1017/S0033291708003632

Vahia, I. V., Palmer, B. W., Depp, C., Fellows, I., Golshan, S., Kraemer, H. C., & Jeste, D. V. (2010). Is late-onset schizophrenia a subtype of schizophrenia? *Acta Psychiatrica Scandinavica*, *122*(5), 414–426. doi:10.1111/j.1600-0447.2010.01552.x

Van Assche, L., Morrens, M., Luyten, P., Van de Ven, L., & Vandenbulcke, M. (2017). The neuropsychology and neurobiology of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: A critical review. *Neuroscience and Biobehavioral Reviews*, *83*, 604–621. doi:10.1016/j.neubiorev.2017.08.024

Van Assche, L., Van Aubel, E., Van de Ven, L., Bouckaert, F., Luyten, P., & Vandenbulcke, M. (2019). The neuropsychological profile and phenomenology of late onset psychosis: A Cross-sectional study on the differential diagnosis of Very-Late-Onset Schizophrenia-Like psychosis, dementia with Lewy bodies and Alzheimer's type dementia with psychosis. *Archives of Clinical Neuropsychology*, *34*(2), 183–199. doi:10.1093/arclin/acy034

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., … Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophrenia Bulletin*, *38*(4), 661–671. doi:10.1093/schbul/sbs050

Wake, R., Miyaoka, T., Araki, T., Kawakami, K., Furuya, M., Limoa, E., … Horiguchi, J. (2016). Regional cerebral blood flow in late-onset schizophrenia: a SPECT study using 99mTc-ECD. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(1), 3–12. doi:10.1007/s00406-015-0607-z

Zakzanis, K. K., Andrikopoulos, J., Young, D. A., Campbell, Z., & Sethian, T. (2003). Neuropsychological differentiation of late-onset schizophrenia and dementia of the Alzheimer's type. *Applied Neuropsychology*, *10*(2), 105–114. doi:10.1207/S15324826AN1002_06

Zakzanis, K. K., Kielar, A., Young, D. A., & Boulos, M. (2001). Neuropsychological differentiation of late onset schizophrenia and frontotemporal dementia. *Cogn Neuropsychiatry*, *6*(1), 63–77. doi:10.1080/13546800042000052