The incidence of very late-onset psychotic disorders: a systematic review and meta-analysis, 1960-2016

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Abstract

A substantial subset of people with psychotic disorders are first diagnosed in old age, yet little is known about the epidemiology of very-late-onset schizophrenia-like psychosis. We investigated the incidence of affective and non-affective psychotic disorders in those aged 65 and above, and examined variation related to potential risk factors via systematic literature review.

We searched PubMed, PsychInfo, Web of Science and bibliographies and directly contacted authors to obtain citations published between 1960-2016 containing (derivable) incidence data. Cases were those diagnosed with non-organic psychotic disorders after age 65. Findings were presented narratively, and random-effects meta-analyses were used to obtain pooled incidence rates.

From 5685 citations, 41 met inclusion criteria. The pooled incidence of: affective psychoses was 30.9 per 100,000 person-years at-risk (100kpy) (95% CI: 11.5–83.4; I^2= 0.99), and: schizophrenia was 7.5 per 100kpy (95% CI: 6.1–9.1; I^2= 0.98), with some evidence of higher schizophrenia rates in women (odds ratio [OR]=1.6; 95% CI: 1.0-2.5, p=0.05). We found narrative evidence of increasing incidence rates of non-affective psychoses with age, and higher rates amongst migrants than baseline populations, but no evidence that incidence varied by study quality or case ascertainment period (quality OR=1.04; 95% CI: 0.74-1.48; time period OR=1.00; 95% CI: 0.95–1.05).

Substantial heterogeneity in incidence of very late onset schizophrenia-like psychoses was observed. No identified studies examined possible risk factors which may account for such variation, including socio-economic status, sensory impairment, traumatic life events, or social isolation.

Introduction

Psychotic disorders typically emerge during adolescence or early adulthood (Kessler et al., 2007), yet research suggests that a substantial minority have a first episode in old age (Howard et al., 2000). However, compared with earlier adult-onset psychosis, little is known about the epidemiology of very late-onset schizophrenia-like psychosis (VLOSLP).

Compared with psychotic disorders with a younger age-at-onset, VLOSLP has consistently been found to be more common in women than men (Almeida et al., 1995; Castle and Murray, 1991; Howard et al., 1994). VLOSLP patients also have higher levels of premorbid functioning across educational and occupational domains (Castle et al., 1997), lower morbid psychosis risk amongst relatives (Howard et al., 1997), and differing symptomatology, with fewer negative symptoms, compared to those with an earlier age-at-onset (Almeida et al., 1995). Several potential risk factors have been associated with VLOSLP, including: hearing impairment (Cooper et al., 1974; Cooper and Curry, 1976), visual impairment (Cooper and Porter, 1976), early adversity (Fuchs, 1994; Fuchs, 1999; Gurian et al., 1992; Reulbach et al., 2007), social isolation (Kay and Roth, 1961; Pearlson et al., 1989) and premorbid schizotypal traits (Kay and Roth, 1961). However, these findings have not consistently replicated and epidemiological support for this is lacking (Brunelle et al., 2012).

Most studies of risk factors for VLOSLP have been cross-sectional, with small, unrepresentative samples, making it difficult to draw valid conclusions. Further, most epidemiological research has focused on psychotic disorders beginning before 65 years old, meaning that the epidemiology of psychotic disorders in older adults has remained relatively neglected. Most epidemiological studies of VLOSP have focused on prevalence, with 1-year estimates ranging from 0.1%-0.5% (Howard et al., 2000), with less research on incidence and how this varies in relation to putative risk factors for VLOSLP. Synthesizing current evidence

on the incidence of VLOSLP may highlight consistent themes which could help to provide insight into the etiology of late-life psychosis, or gaps in the literature requiring examination.

Aims and hypotheses

We aimed to synthesize the literature on the incidence of very late-onset affective and non-affective psychotic disorders, and how this varied by age and sex. Consistent with the previous literature, we hypothesized that the incidence of very late-onset psychotic disorders would increase with age, and would be higher amongst women than men. Additionally, where data were available, we sought to explore variation in incidence by family history of psychopathology, socioeconomic status (SES), ethnicity, migrant status, sensory impairment, social isolation, marital status, education, employment history, sensory impairment and traumatic life events. We expected higher incidence rates amongst migrant groups, given similar findings in younger adults (Kirkbride et al., 2012), and amongst those with: a family history of psychotic disorders, lower SES, the experience of traumatic life events, and sensory impairment.

Methods

We conducted this systematic review following PRISMA guidelines (Moher et al., 2009; see Supplementary Table 1), including pre-registering our protocol (http://www.crd.york.ac.uk/PROSPERO, registration number: CRD42016035720).

Search strategy

We systematically searched PubMed, PsychInfo and Web of Science databases using terms covering three main areas: “late-onset”, “incidence” and “psychosis” (see Supplementary Figure 1). We adapted search terms for each database using database-specific MeSH headings. We searched bibliographies of included citations and directly contacted authors to

request data, where appropriate. We restricted our review to English language papers published between January 1960 and March 2016.

Eligibility criteria

Although VLOSLP usually refers to those aged over 60 years, we restricted our search to those aged 65 years and older because this is typically the upper age cut-off in epidemiological studies of "adult-onset" psychosis, which have been widely reviewed (Kirkbride et al., 2012; McGrath et al., 2004; Van der Werf et al., 2012). Other eligibility criteria were as follows:

1. Contained incidence data, or data from which incidence rates could be derived (numerator and denominator).
2. Attempted to conduct a population-based epidemiological study, irrespective of quality (see below).
3. Cases first diagnosed with psychotic disorders after age 65 (incident cases).
4. Excluded those with dementia, organic or drug-induced psychoses.

Screening

We screened citation titles to assess whether they met eligibility criteria, with definite or possible citations forwarded to abstract, and subsequently, full text review. One researcher (JS) screened studies and extracted data. A second researcher (JBK) screened a randomly-selected 10% sample, with 99.8% inter-rater agreement, Cohen's $k = 0.88$, $p=<.001$.

Database management and data extraction

We stored extracted data in a spreadsheet, adapted from a previous systematic review (Kirkbride et al., 2012). Data were divided into study-level data about study characteristics,

rate-level data about incidence rates, and meta-level data on time period and study quality (see below).

Exposures and outcomes

Our primary outcome was the incidence per 100,000 person-years at-risk of a non-organic psychotic disorder in those aged 65 and above. Included studies used a range of diagnostic classifications, including ICD-8 to ICD-10, DSM-III-R, and DSM-IV. Although the classification of psychotic disorders varies between diagnostic classifications and editions, we assumed sufficient commonalities to pool citations according to the following diagnostic outcomes: i) non-affective psychotic disorders (ICD-10 F20-F29 or equivalent, including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and brief and unspecified psychoses), ii) schizophrenia (ICD-10 F20 or equivalent), iii) affective psychoses (ICD-10 F30-39 or equivalent, excluding depression without psychosis).

Where available, we extracted incidence data in relation to the following exposures: age, sex, ethnicity, socio-economic status (SES), migrant status, marital status, education, employment, sensory impairment such as deafness or blindness, traumatic life events (childhood or adulthood), and family history of psychopathology.

Where incidence rates were not explicitly reported, we derived them from ancillary information where possible (i.e. numerator, denominator, standard errors). Where citations reported overlapping data from the same study, the rate or citation providing the most pertinent information for each specific analysis was considered primary.

Study quality

Two independent raters (JS, JBK), rated study quality according to 5 criteria, with 87% inter-rater agreement, Cohen's $k = 0.61$, $p=<.001$. Discrepancies were dealt with via consensus

agreement. We used a quality scale adapted from a previous systematic review (Kirkbride et al., 2012) to assess five key indicators of epidemiological quality: defined catchment area, accurate denominator, population-based case ascertainment, standardized research diagnoses, and well-defined inclusion and exclusion criteria (see Supplementary Table 2).

Data analysis

We first conducted a narrative synthesis of published incidence data on very-late-onset psychotic disorders, particularly important given the substantial heterogeneity observed between incidence estimates (generally, $I^2 = \geq .90$). Where three or more citations provided incidence data which could be pooled, we conducted random effects meta-analyses using the DerSimonian and Laird (1986) method to obtain pooled estimates. Incidence rates were transformed to their natural logarithm and entered into meta-analyses with corresponding standard errors. Where possible, to allow the pooling of incidence rates for those aged 65 and above, estimates reported from the same citation for different age bands were aggregated into an overall age 65+ rate. We also carried out random-effects meta-regressions to explore whether variation in incidence was associated with sex, study quality, or case ascertainment period. We examined evidence of publication bias via visual inspection of funnel plots and formal testing using Egger's test of bias. We conducted meta-analyses in Stata version 13 using the *metan* command. Funnel plots and Egger's bias test were conducted using *metafunnel* and *metabias* packages. Random-effects meta-regressions were conducted using the *metareg* package.

Results

We retrieved 5685 citations, of which 41 – published between 1967 and 2014 – met eligibility criteria (Figure 1; Table 1; Supplementary Figure 2). Four authors provided original data (Bogren et al., 2010; Pedersen et al., 2014; Van Os et al., 1995; Baldwin et al.,

2005) and Van der Werf et al., (2012) provided further unpublished data from studies ascertained as part of a previous systematic review.

<Figure 1 about here>

Included studies covered case ascertainment periods ranging from 1926 to 2010 (Andersen & Hynnekleiv, 2007; Baldwin et al., 2005 [including unpublished supplemental data]). Most citations reported incidence across the lifespan, whereas only eight focused specifically on older adults (Castle et al., 1993; Copeland et al., 1998; Holden, 1987; Mitford et al., 2010; Mitter et al., 2004; Mitter et al., 2005; Reeves et al., 2001; Van Os et al., 1995). We rated 22% of citations as high quality (rated 4-5), 71% as average quality (rated 2-3), and 7% as poor quality (rated 0-1) (see Table 1).

151 <Table 1 about here>

Incidence by age and sex

Non-affective psychotic disorders

Seven citations reported the incidence of non-affective psychotic disorders in older adults (Bogren et al., 2010; Mitford et al., 2010; Mitter et al., 2004; Mitter et al., 2005; Pedersen et al., 2014; Reeves et al., 2001; Van Os et al., 1995). Studies were conducted in Sweden, England, Wales and Denmark, and were rated as high (29%) or average (71%) quality. Three non-overlapping studies provided overall incidence rates of non-affective psychotic disorders in those aged 65 and above (Mitford et al., 2010; Mitter et al., 2004; Reeves et al., 2001). The reported incidence of non-affective psychotic disorders in Northumberland was 14.3 per 100kpy (95% CI: 10.5-18.1) in those aged 65 and above, compared with 17.8 (95% CI: 15.5-20.0) in those aged below 65 (Mitford et al., 2010). A study conducted in Tower Hamlets, London, provided a rate of 31.4 per 100kpy (95% CI: 25.4–38.8) (Mitter et al., 2004), and in Camberwell, London, a rate of 39.9 per 100kpy (95% CI: 31.1–51.3) was reported in those aged 60 and above (Reeves et al., 2001).

Incidence was higher amongst older women than men in five studies reporting rates of non-affective psychotic disorders by sex (Bogren et al., 2010; Mitter et al., 2004; Pedersen et al., 2014; Reeves et al., 2001; Van Os et al., 1995). Three studies reporting incidence by age provided evidence of increasing rates with older age (Mitter et al., 2005; Pedersen et al., 2014; Van Os et al., 1995). In a study conducted in Denmark, incidence peaked in younger adulthood, followed by an additional increase after age 65 (Pedersen et al., 2014). Another study reported increasing rates from age 60 in both sexes in England, Wales and the Netherlands (Van Os et al., 1995), while Mitter et al. (2005) reported a slight decrease in incidence with age amongst older men, but substantial increases for women.

Schizophrenia

We identified 23 non-overlapping citations conducted between 1926 and 2010 providing data on the incidence of schizophrenia amongst older adults (Adelstein et al., 1968; Ajdacic-Gross et al., 2007; Allardyce et al., 2000; Andersen & Hynnekleiv, 2007; Baldwin et al., 2005; Bamrah et al., 1991; Bland, 1977; Bogren et al., 2010; Boydell et al., 2003; Copeland et al., 1998; de Alarcon et al., 1993; De Salvia et al., 1993; Gater et al., 1995; Geddes et al., 1993; Helgason, 1977; Malzberg, 1967; Pedersen et al., 2014; Proctor et al., 2004; Salokangas, 1979; Thornicroft et al., 1993; Thorup et al., 2007; Van Os et al., 1995; Welham et al., 2004). Quality ranged from low (4%), to average (74%) or high (22%). Eight citations were excluded from the meta-analysis as they provided data on overall incidence aged 60+, rather than aged 65+ (Adelstein et al., 1968; Ajdacic-Gross et al., 2007; Allardyce et al., 2000; Andersen & Hynnekleiv, 2007; Bland, 1977; Proctor et al., 2004; Salokangas, 1979; Thorup et al., 2007) (see Supplementary Figures 3-5 for additional analyses including these citations). Another citation was excluded due to including a provisional case who did not meet full DSM-III-R criteria (Copeland et al., 1998). This citation reported a rate of 3 per 100kpy (95% CI: 0 – 110.7) in Liverpool. Three citations could not provide an age 65+ rate due to lack of corresponding standard errors and/or sample size data, although findings on incidence by age and sex are reported in the following sections (Bamrah et al., 1991; Malzberg, 1967; Pedersen et al., 2014).

The remaining 11 citations provided 26 estimates (due to several citations reporting separate estimates for different time periods) of schizophrenia incidence in those aged 65 and above, which could be pooled in a meta-analysis (Baldwin et al., 2005; Bogren et al., 2010; Boydell et al., 2003; de Alarcon et al., 1993; De Salvia et al., 1993; Gater et al., 1995; Geddes et al., 1993; Helgason, 1977; Thornicroft et al., 1993; Van Os et al., 1995; Welham et al., 2004).

Quality was average (73%) or high (27%). The pooled incidence of schizophrenia was 7.5 per 100kpy (95% CI: 6.2-9.1; I^2= 0.98) (Figure 2).

<Figure 2 about here>

Estimates ranged from 3.3 per 100kpy (95% CI: 2.5–4.4) in Scotland (Geddes et al., 1993) to 30.31 per 100kpy (95% CI: 33.4–62.1) in Australia (Welham et al., 2004). Pooled rates were higher in women than men, based on 41 estimates from 8 suitable citations (women: 8.6 per 100kpy; 95% CI: 6.9-10.6; I^2= 0.98, men: 5.4 per 100kpy; 95% CI: 4.2–6.9, I^2= 0.96) (Figure 3) (Bogren et al., 2010; Boydell et al., 2003; de Salvia et al., 1993; Geddes et al., 1993; Helgason, 1977; Van Os et al., 1995; Baldwin et al., 2005; Welham et al., 2004). A meta-regression indicated that this sex difference approached statistical significance (OR= 1.6, 95% CI: 1.0-2.5, p=.052). Visual inspection of funnel plots of standard error against log incidence rates and formal testing via Egger's test did not provide evidence of publication bias (p=0.9) (Supplementary Figure 6).

<Figure 3 about here>

Fifteen citations reported the incidence of schizophrenia by age and sex (Adelstein et al., 1968; Ajdacic-Gross et al., 2007; Allardyce et al., 2000; Andersen & Hynnekleiv, 2007; Bland, 1977; Bamrah et al., 1991; Bogren et al., 2010; Boydell et al., 2003; Geddes et al., 1993; Helgason, 1977; Pedersen et al., 2014; Proctor et al., 2004; Van Os et al., 1995; Baldwin et al., 2005; Welham et al., 2004). While incidence mostly peaked amongst younger adults, (e.g. Helgason, 1977; Pedersen et al., 2014; Proctor et al., 2004) the pattern amongst older adults varied considerably across studies. Three citations broadly found increasing rates with age for men and women after age 65, (Allardyce et al., 2000; Boydell et al., 2003; Proctor et al., 2004) whereas three citations reported decreases with age (Andersen & Hynnekleiv, 2007; Bland, 1977; Pedersen et al., 2014). One paper reported relatively stable

rates with age, although few cases were identified (Bogren et al., 2010). In a study conducted in Salford (UK), incidence increased up to age 80 in both sexes, followed by a decline, (Adelstein et al., 1968) whereas in a study in Queensland (Australia), incidence decreased from age 65 to 75, followed by an increase in both sexes (Welham et al., 2004). In several studies no consistent pattern emerged by age (Baldwin et al., 2005; Helgason, 1977), or mixed findings were observed over time (Ajdacic-Gross et al., 2007; Bamrah et al., 1991; Geddes et al., 1993; Van Os et al., 1995).

Affective psychoses

11 non-overlapping citations provided data on the incidence of affective psychoses in older adults (Adelstein et al., 1968; Baldwin et al., 2005; Bland, 1977; Bogren et al., 2010; de Alarcon et al., 1993; Eagles, 1985; Helgason, 1977; Mitford et al., 2010; Salokangas, 1979; Spicer et al., 1973; Welham et al., 2004). Studies were conducted between 1951 and 2010 and quality was average (91%) or high (9%). Studies were conducted in England, Wales, Scotland, Ireland, Finland, Iceland, Canada, Australia and Costa Rica.

Five citations provided sufficient data to estimate an overall rate of affective psychosis in those aged 65 and above (95% CI: 11.5–83.4; I^2= 0.99; Figure 4) (Baldwin et al., 2005; de Alarcon et al., 1993; Helgason, 1977; Mitford et al., 2010; Welham et al., 2004). Four of these citations used ICD-8 and -9 diagnostic codes 296 and one used ICD-10 codes F30-F32.3. Four estimates lay between 10.1 per 100kpy (95% CI: 7.3–13.8) (Mitford et al., 2010), to 25.9 (95% CI: 22.5–29.8) (de Alarcon et al., 1993), with one study in Iceland reporting a substantially higher rate (268.9 per 100kpy; 95% CI: 218.7–330.6) (Helgason, 1977). Two further citations could not be included in the meta-analysis (Bland, 1977; Bogren et al., 2010). Bogren et al. (2010) only provided incidence data on more narrowly defined psychotic depression (excluding transient affective psychoses and bipolar disorder with psychosis): no

cases of psychotic depression were identified in older males, whereas the rate for females was 16 per 100kpy (95% CI: 4.0–64.2). Bland (1977) reported an estimated incidence of affective psychoses in those aged 60 and above (rather than age 65) of 34.6 per 100kpy (95% CI: 32.4–36.9).

<Figure 4 about here>

Three citations provided six estimates of the incidence of affective psychoses by sex (Baldwin et al., 2005; Helgason, 1977; Welham et al., 2004). Pooled incidence was higher amongst women (50.3 per 100kpy; 95% CI: 6.4–396.9; I^2= 0.99) than men (35.1; 95% CI: 9.8–125.5; I^2= 0.97), although confidence intervals around these estimates were wide, partially driven by the Icelandic study (Helgason, 1977) (Supplementary Figure 7). There was no evidence from meta-regression that the incidence of affective psychosis differed between older men and women (OR= 1.22, 95% CI: 0.03–49.35).

Eleven citations reported rates of affective psychoses amongst both younger and older adults (Adelstein et al., 1968; Baldwin et al., 2005; Bland, 1977; Bogren et al., 2010; de Alarcon et al., 1993; Eagles & Whalley, 1985; Helgason, 1977; Mitford et al., 2010; Salokangas, 1979; Spicer et al., 1973; Welham et al., 2004). Interestingly, five citations reported the highest rates in older adults compared with amongst younger adults (de Alarcon et al., 1993; Eagles & Whalley, 1985; Helgason, 1977; Mitford et al., 2010; Salokangas, 1979). Two further studies reported the highest rates of more narrowly defined psychotic depression after age 65 (Adelstein et al., 1968; Bogren et al., 2010). Conversely, three studies reported highest rates of affective psychoses amongst young or middle-aged adults (Baldwin et al., 2005; Bland, 1977; Welham et al., 2004). After age 65, four citations reported a decrease in incidence with age (Adelstein et al., 1968; Bland, 1997; Helgason, 1977; Spicer et al., 1973), which was more substantial amongst women in two studies (Adelstein et al., 1968; Helgason, 1977).

One study broadly reported increased incidence in older men, but a slight decrease with age in women (Eagles & Whalley, 1985). No consistent pattern by age emerged in two further studies (Baldwin et al., 2005; Welham et al., 2004).

Incidence by migrant status

Only five non-overlapping studies reported incidence by migrant status (Cochrane and Bal, 1987; Malzberg, 1967; Mitter et al., 2004; Mitter et al., 2005; Reeves et al., 2001). These studies related to non-affective psychotic disorders (Mitter et al., 2004; Mitter et al., 2005; Reeves et al., 2001), or schizophrenia (Cochrane and Bal, 1987; Malzberg, 1967). Studies were conducted between 1960 and 2003 and were of average (60%) or high quality (40%). The incidence of non-affective psychotic disorders in older adults was generally substantially higher for those of black ethnicities compared with baseline populations (those of white British ethnicity) (Cochrane and Bal, 1987; Mitter et al., 2004; Reeves et al., 2001), whereas the pattern was less consistent amongst Asian migrants. For example, Mitter et al. (2004) reported a higher incidence amongst black elders in Tower Hamlets, 260 per 100kpy (95% CI: 55–750), compared with an incidence of 32 per 100kpy amongst white elders (95% CI: 20–45). Conversely, incidence was lower amongst Bangladeshi elders (25 per 100kpy; 95% CI: 4-89). A higher incidence of schizophrenia was reported amongst white migrants to New York State from other regions of the USA compared with those born in New York State between ages 65-74, although this was not observed in those aged 75 and above (Malzberg, 1967).

Incidence by time period and study quality

Given the substantial heterogeneity observed between estimates, we examined whether the incidence of any outcomes varied by time period of case ascertainment or study quality. It was only possible to carry out meta-regressions on overall incidence rates of schizophrenia

(N=11) and affective psychoses (N=5), due to insufficient data in other categories. Variation in study quality amongst these citations was slightly narrower than variation across citations included in the entire study [Study quality: Schizophrenia [N=11]: average (73%), high (27%). Affective psychosis [N=5]: average (80%), high (20%). All citations [N=41]: poor (7%), average (71%) or high (22%)] (see Table 1).

Using random-effects meta-regressions, we found no evidence that study quality or time of case ascertainment (using mid-year) influenced incidence rates of schizophrenia or affective psychosis in those aged 65 and above [Study quality: Schizophrenia OR= 1.37 (95% CI: 0.32 – 6.78), Affective psychosis: 1.04 (95% CI: 0.74 – 1.49)], [Case ascertainment period: Schizophrenia: OR= 0.92 (95% CI: 0.83 – 1.02), Affective psychosis: OR= 1.00 (95% CI: 0.95 – 1.05)].

Discussion

Summary of principal findings

In the largest systematic review of the incidence of very-late onset schizophrenia-like psychosis to date, we found evidence of a substantial burden of disorder which increased with age after 65 years old. Our review revealed substantial heterogeneity in estimates of incidence, which may have been driven by the relative absence of robust epidemiological studies in this field compared with adult-onset psychosis. Where the evidence was most consistent, we found higher rates of non-affective psychosis, including schizophrenia in older women than men, and higher rates of non-affective psychosis in migrant groups. The overall pooled incidence of affective psychosis reported in those over 65 years was high. We failed to identify any epidemiological study which had investigated the incidence of VLOSLP by several putative risk factors, including socioeconomic status, social isolation or sensory impairments. Taken together, these findings point towards a lack of a robust epidemiological

evidence base important in informing etiology and public mental health about variation in the incidence of VLOSLP.

Strengths and weaknesses

To our knowledge this is the first study to systematically review the literature on the incidence of affective and non-affective psychotic disorders specifically amongst older adults. Strengths of this review include pre-registration of our study and a thorough literature search involving comprehensive search terms, bibliography searches and contacting authors directly to request additional data. We used strict eligibility criteria, including only epidemiological studies focused on new cases of psychotic disorders in old age.

We noted some limitations inherent to the studies included in this review. First, many citations did not provide standard errors or confidence intervals around estimates, limiting insight into the precision of estimates and preventing the pooling of incidence rates. Second, variation in age bands across studies hindered our ability to pool some estimates. Third, although we rated few studies as poor, certain quality criteria were consistently lacking across studies. For example, only 30% of included studies attempted to validate diagnoses against operationalized research criteria, which may have affected their validity and contributed to the high levels of between-study heterogeneity observed here. Additionally, only 5% of studies took a population-based approach to case ascertainment, with reliance on hospital admissions common across studies, which may have led to underestimates of incidence.

Several limitations of our review should also be considered. First, pooled incidence rates should be interpreted cautiously, and alongside our narrative review, given high levels of heterogeneity between estimates. Second, due to our inclusion of only published English language papers, we may have missed relevant unpublished papers and those published in other languages, although findings from our funnel plot and Egger's test did not indicate

publication bias. Third, although we examined incidence in relation to study quality, there was a high tendency to the mean amongst quality ratings, which may have influenced findings about the lack of association between incidence and study quality.

Meaning of findings

The lack of epidemiological research focused on VLOSLP incidence highlights the need for further high quality, primary research examining incidence variation in relation to a range of potential risk factors for VLOSLP, including socio-economic status, sensory impairment, social isolation and traumatic life events. This could have important implications for our understanding of the etiology of VLOSLP and could help to inform public mental health and service commissioning and planning.

The relatively low incidence of schizophrenia observed amongst older adults in this review (vis-à-vis younger adults) could reflect 'true' rates in this group. Overall rates of non-affective psychotic disorders identified in this review were substantially higher than those for schizophrenia alone, suggesting that older adults are more likely to be diagnosed with other non-affective psychotic disorders, perhaps due to atypical clinical presentation; such patients often present as highly delusional, but lacking negative symptoms and thought disorder (Pearlson et al., 1989). Alternatively, given that many included citations did not attempt to ascertain cases from the community and often relied on hospital admissions, it is possible that some studies underestimated the true incidence of very late-onset schizophrenia-like psychoses. This bias could be particularly problematic in older adults experiencing psychotic phenomena, given that they may be less likely to contact services due to higher levels of functioning (Kay and Roth, 1961), and a lack of social contact (Castle and Murray, 1993). Our study found relatively high rates of affective psychoses after age 65 years old, which again may reflect differing symptomatic presentation of psychotic disorders in later life.

Our finding of higher incidence rates of non-affective psychotic disorders amongst older women compared with men distinguishes psychotic disorders with late-onset from those with an earlier age-at-onset. Data from this review suggest that the previously identified peak in incidence amongst women in middle age (Coid et al., 2008; Häfner et al., 1993) may be maintained into older age. The mechanisms underlying the higher rates of psychosis observed in middle aged and older women are unclear. It is possible that changing social roles and demands experienced by women in middle age and later in life could be implicated. Additionally, the anti-dopaminergic properties of estrogen may operate as a protective factor against the development of psychosis in younger women, and the drop in estrogen in middle-age could lead to an increased risk of psychosis (Häfner, 2003; Riecher-Rössler and Häfner, 1992).

VLOSLP incidence was generally higher amongst migrant groups than baseline populations, which corresponds with the literature on psychosis in adults under age 65 (Kirkbride et al., 2012). Various potential explanations for this association have been put forward, including stressors experienced prior to, during, and post-migration (Cantor-Graae et al., 2003; Kirkbride et al., 2012; Morgan & Hutchinson, 2009; Veling et al., 2007). Further research is needed to examine the association between migration and psychosis incidence in older adults and to explore whether migration imparts the same social stressors on older adults as at other ages.

Conclusion

Our research highlighted a substantial and increasing incidence of disorder after 65 years old, with some evidence of higher rates in women and migrants. The dearth of research on other putative risk factors for VLOSLP, such as sensory impairments, socioeconomic status or social adversities highlight the need for further high quality research designed to precisely

delineate the descriptive epidemiology of different psychotic disorders in older adults using large population-based cohorts. Only via robust, evidence-based research will it be possible to provide appropriate mental health services for those who experience a first-episode of psychosis later in life; our study provides some quantification of this burden, but suggests more research is urgently required given the ageing population profiles of many countries.

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Conflicts of interest

None.

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Figure legends

Figure 1. PRISMA flow diagram

Figure 2. Forest plot of incidence rates of schizophrenia in those aged 65 and above. Incidence rate per 100,000 person-years at risk.

Figure 3. Forest plot of incidence rates of schizophrenia in those aged 65 and above by sex. Left: male, right: female. Incidence rate per 100,000 person-years at risk.

Figure 4. Forest plot of incidence rates of affective psychosis in those aged 65 and above. Incidence rate per 100,000 person-years at risk.

Table 1. Citation characteristics table.

Tables and figures

Figure 1.

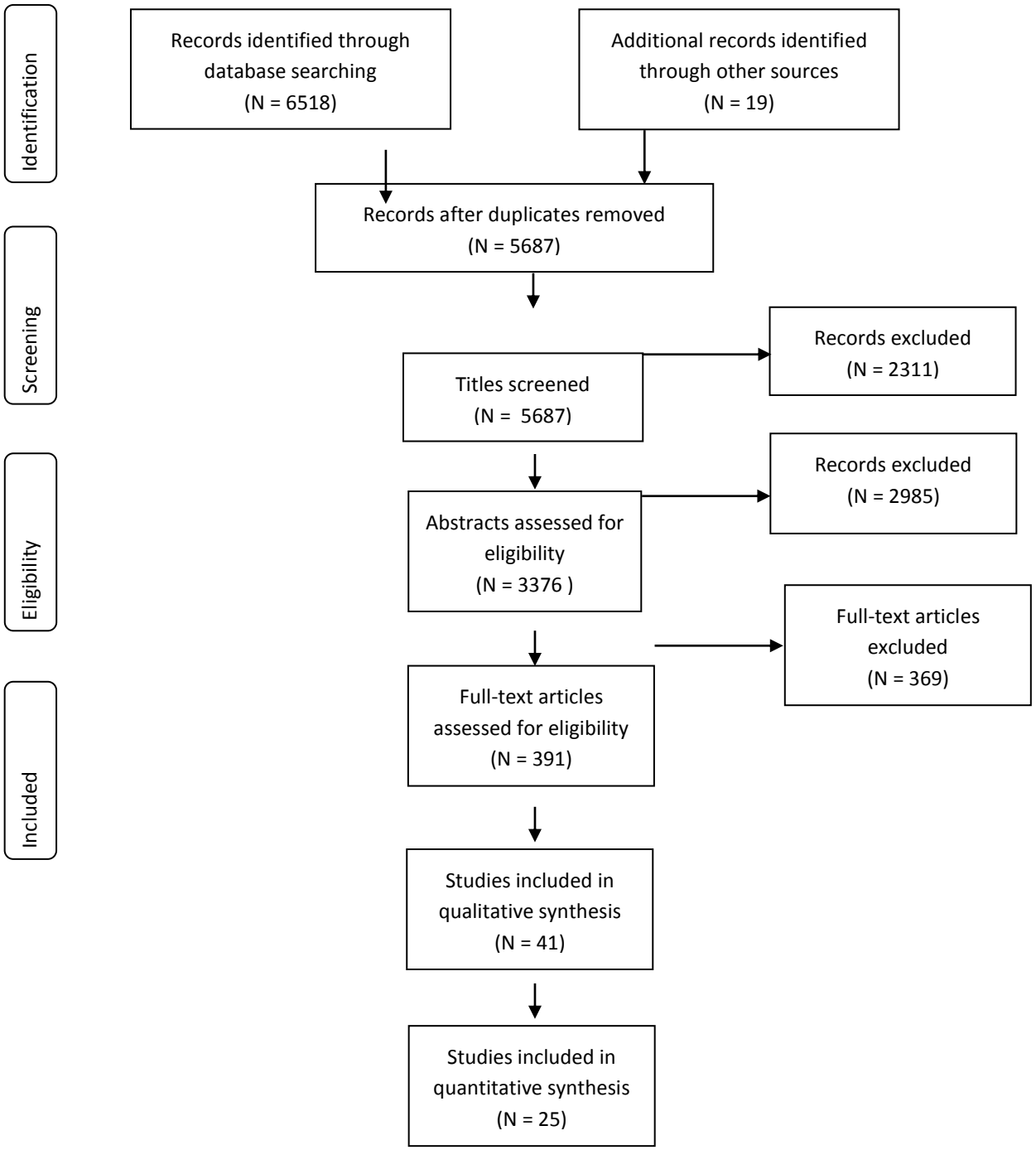
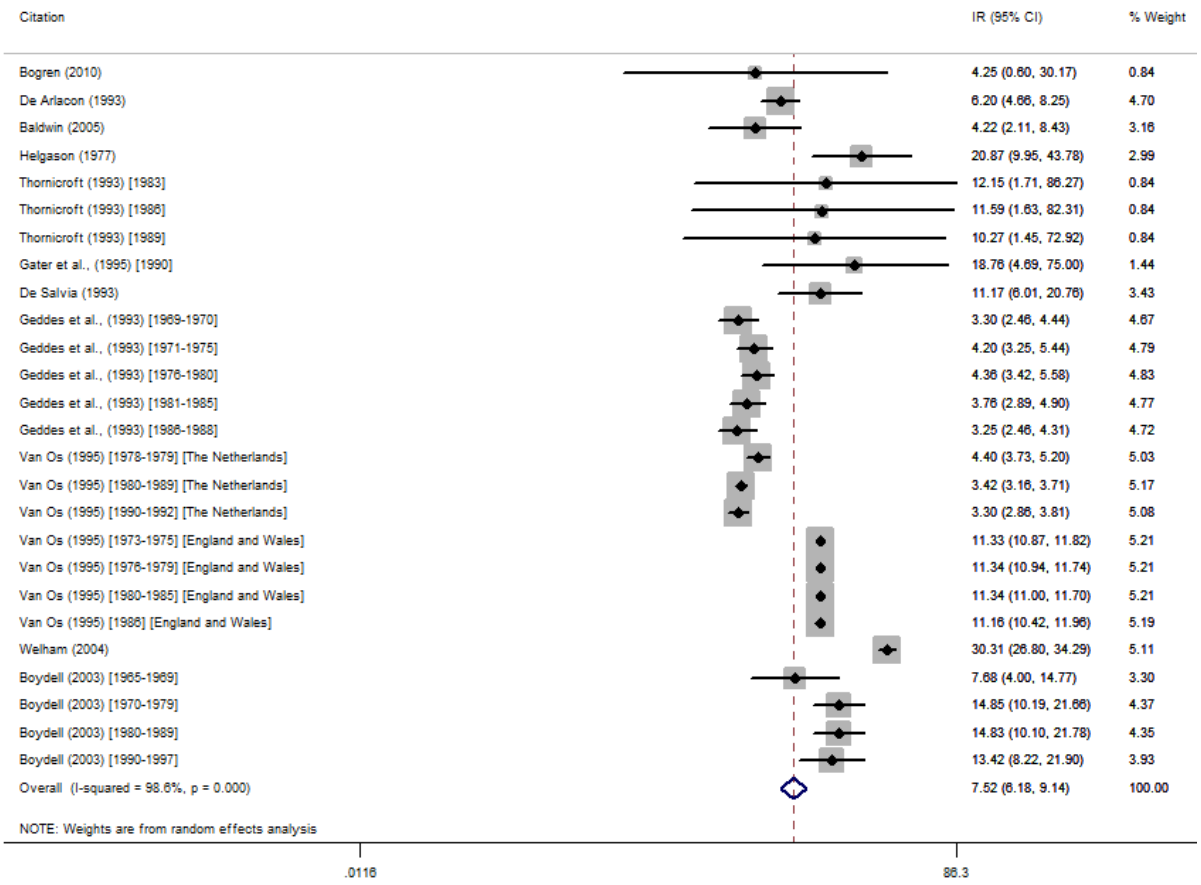


Figure 2.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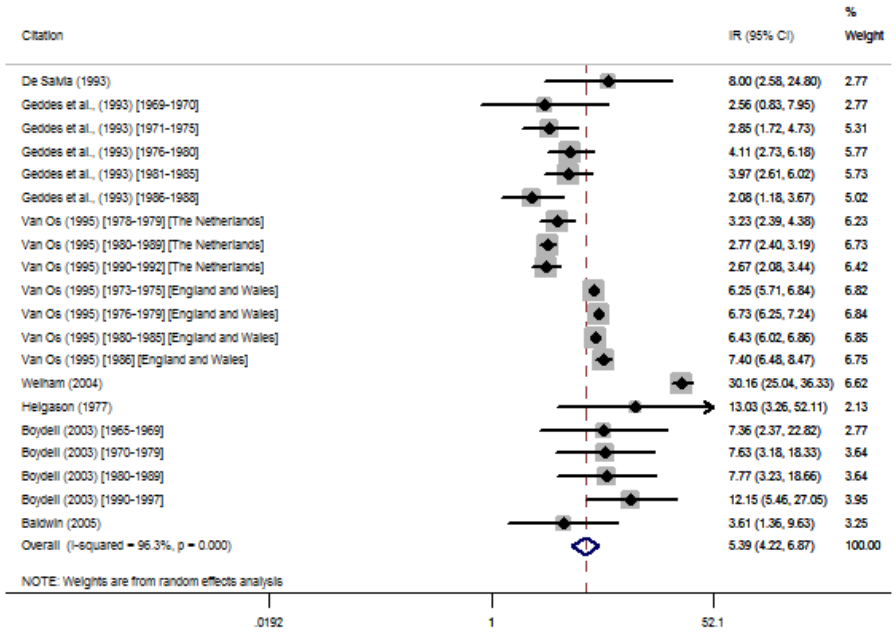
Bogren (2010) 4.25 (0.60, 30.17) 0.84
De Arlacon (1993) 6.20 (4.66, 8.25) 4.70
Baldwin (2005) 4.22 (2.11, 8.43) 3.16
Helgason (1977) 20.87 (9.95, 43.78) 2.99
Thornicroft (1993) [1983] 12.15 (1.71, 86.27) 0.84
Thornicroft (1993) [1986] 11.59 (1.63, 82.31) 0.84
Thornicroft (1993) [1989] 10.27 (1.45, 72.92) 0.84
Gater et al., (1995) [1990] 18.76 (4.69, 75.00) 1.44
De Salvia (1993) 11.17 (6.01, 20.76) 3.43
Geddes et al., (1993) [1969-1970] 3.30 (2.46, 4.44) 4.67
Geddes et al., (1993) [1971-1975] 4.20 (3.25, 5.44) 4.79
Geddes et al., (1993) [1976-1980] 4.36 (3.42, 5.58) 4.83
Geddes et al., (1993) [1981-1985] 3.76 (2.89, 4.90) 4.77
Geddes et al., (1993) [1986-1988] 3.25 (2.46, 4.31) 4.72
Van Os (1995) [1978-1979] [The Netherlands] 4.40 (3.73, 5.20) 5.03
Van Os (1995) [1980-1989] [The Netherlands] 3.42 (3.16, 3.71) 5.17
Van Os (1995) [1990-1992] [The Netherlands] 3.30 (2.86, 3.81) 5.08
Van Os (1995) [1973-1975] [England and Wales] 11.33 (10.87, 11.82) 5.21
Van Os (1995) [1976-1979] [England and Wales] 11.34 (10.94, 11.74) 5.21
Van Os (1995) [1980-1985] [England and Wales] 11.34 (11.00, 11.70) 5.21
Van Os (1995) [1986] [England and Wales] 11.16 (10.42, 11.96) 5.19
Welham (2004) 30.31 (26.80, 34.29) 5.11
Boydell (2003) [1965-1969] 7.68 (4.00, 14.77) 3.30
Boydell (2003) [1970-1979] 14.85 (10.19, 21.66) 4.37
Boydell (2003) [1980-1989] 14.83 (10.10, 21.78) 4.35
Boydell (2003) [1990-1997] 13.42 (8.22, 21.90) 3.93
Overall (I-squared = 98.6%, p = 0.000) 7.52 (6.18, 9.14) 100.00
NOTE: Weights are from random effects analysis
.0116
86.3

Figure 3.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Van Os (1995) [1980-1985] [England and Wales] 6.43 (6.02, 6.86) 6.85
Van Os (1995) [1986] [England and Wales] 7.40 (6.48, 8.47) 6.75
Welham (2004) 30.16 (25.04, 36.33) 6.62
Helgason (1977) 13.03 (3.26, 52.11) 2.13
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Boydell (2003) [1970-1979] 7.63 (3.18, 18.33) 3.64
Boydell (2003) [1980-1989] 7.77 (3.23, 18.66) 3.64
Boydell (2003) [1990-1997] 12.15 (5.46, 27.05) 3.95
Baldwin (2005) 3.61 (1.36, 9.63) 3.25
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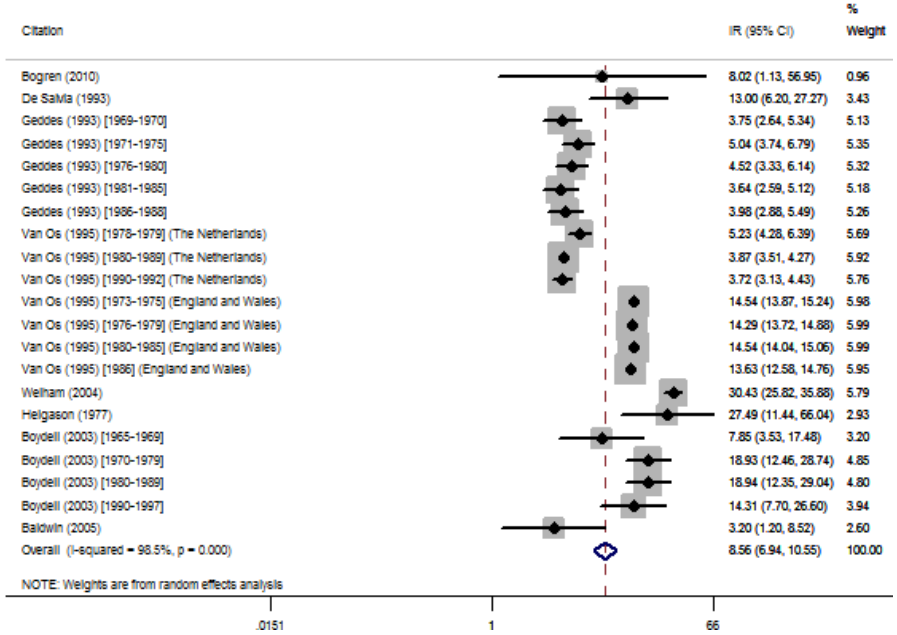
52.1


Citation
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Geddes (1993) [1969-1970] 3.75 (2.64, 5.34) 5.13
Geddes (1993) [1971-1975] 5.04 (3.74, 6.79) 5.35
Geddes (1993) [1976-1980] 4.52 (3.33, 6.14) 5.32
Geddes (1993) [1981-1985] 3.64 (2.59, 5.12) 5.18
Geddes (1993) [1986-1988] 3.98 (2.88, 5.49) 5.26
Van Os (1995) [1978-1979] (The Netherlands) 5.23 (4.28, 6.39) 5.69
Van Os (1995) [1980-1989] (The Netherlands) 3.87 (3.51, 4.27) 5.92
Van Os (1995) [1990-1992] (The Netherlands) 3.72 (3.13, 4.43) 5.76
Van Os (1995) [1973-1975] (England and Wales) 14.54 (13.87, 15.24) 5.98
Van Os (1995) [1976-1979] (England and Wales) 14.29 (13.72, 14.88) 5.99
Van Os (1995) [1980-1985] (England and Wales) 14.54 (14.04, 15.06) 5.99
Van Os (1995) [1986] (England and Wales) 13.63 (12.58, 14.76) 5.95
Welham (2004) 30.43 (25.82, 35.88) 5.79
Helgason (1977) 27.49 (11.44, 66.04) 2.93
Boydell (2003) [1965-1969] 7.85 (3.53, 17.48) 3.20
Boydell (2003) [1970-1979] 18.93 (12.46, 28.74) 4.85
Boydell (2003) [1980-1989] 18.94 (12.35, 29.04) 4.80
Boydell (2003) [1990-1997] 14.31 (7.70, 26.60) 3.94
Baldwin (2005) 3.20 (1.20, 8.52) 2.60
Overall (I-squared = 98.5%, p = 0.000) 8.56 (6.94, 10.55) 100.00
NOTE: Weights are from random effects analysis
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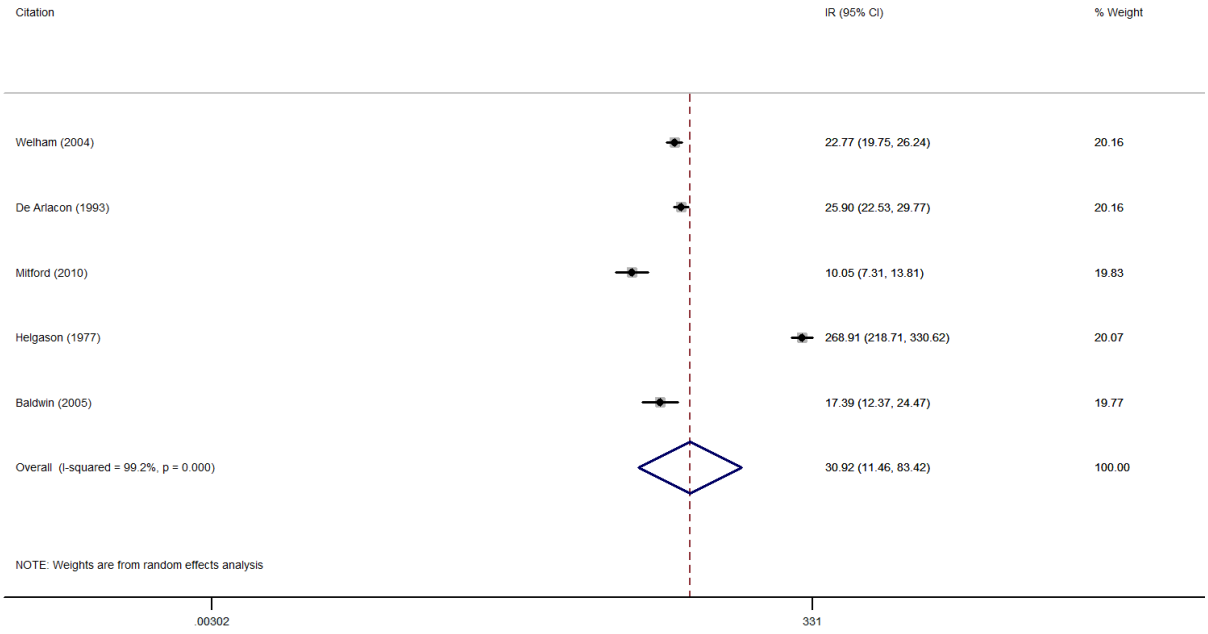
1
66

Figure 4.


Citation
IR (95% CI)
% Weight
Welham (2004)
22.77 (19.75, 26.24)
20.16
De Arlacon (1993)
25.90 (22.53, 29.77)
20.16
Mitford (2010)
10.05 (7.31, 13.81)
19.83
Helgason (1977)
268.91 (218.71, 330.62)
20.07
Baldwin (2005)
17.39 (12.37, 24.47)
19.77
Overall (I-squared = 99.2%, p = 0.000)
30.92 (11.46, 83.42)
100.00
NOTE: Weights are from random effects analysis
.00302
331

Supplementary Figures

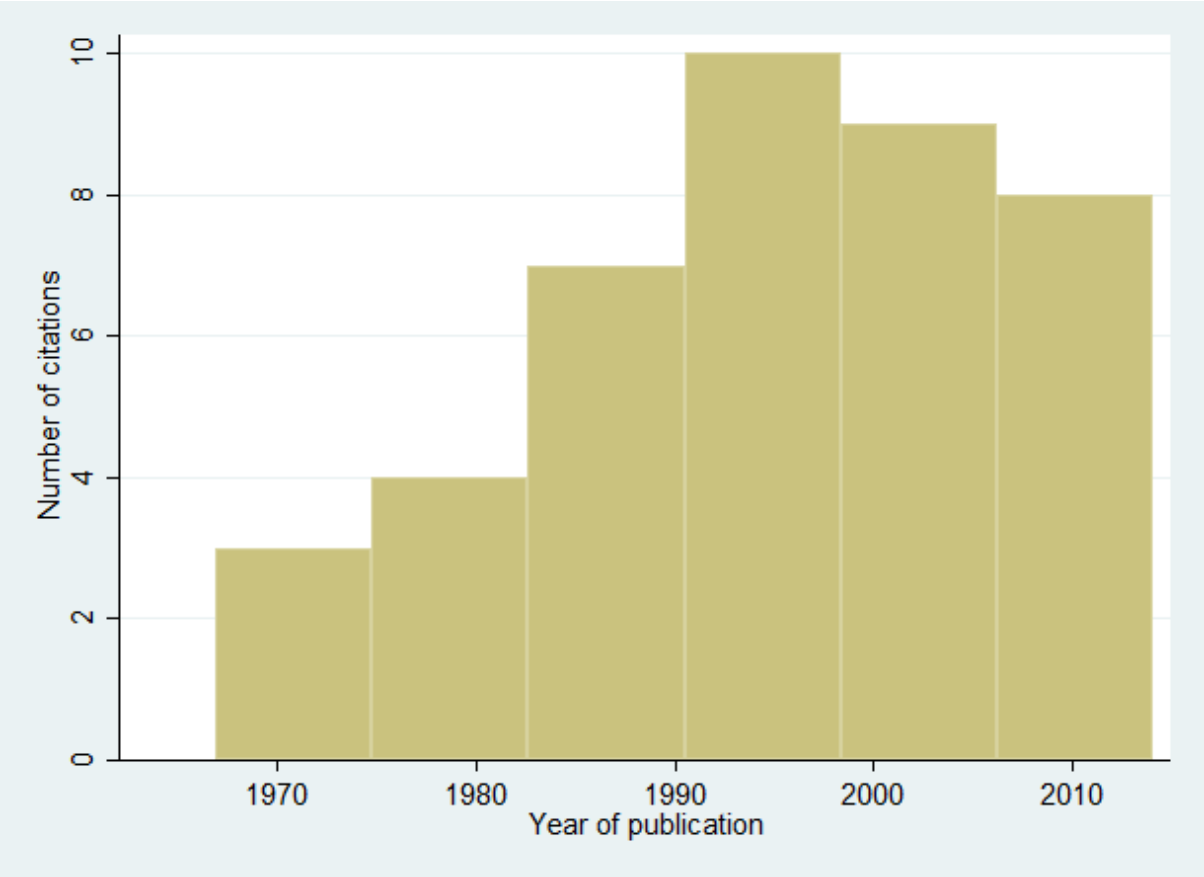
Supplementary Figure 1: Search terms for PsychINFO

Late-onset:
1. MeSH: Geriatrics
2. 'Late-onset'
3. LOP
4. VLOSLP
5. 'Very late-onset'
6. 'Late life'
7. 'Later life'
8. Aging
9. Ageing
10. Geriatric
11. 'Old age'
12. 'Older age'
13. 'Older adult'

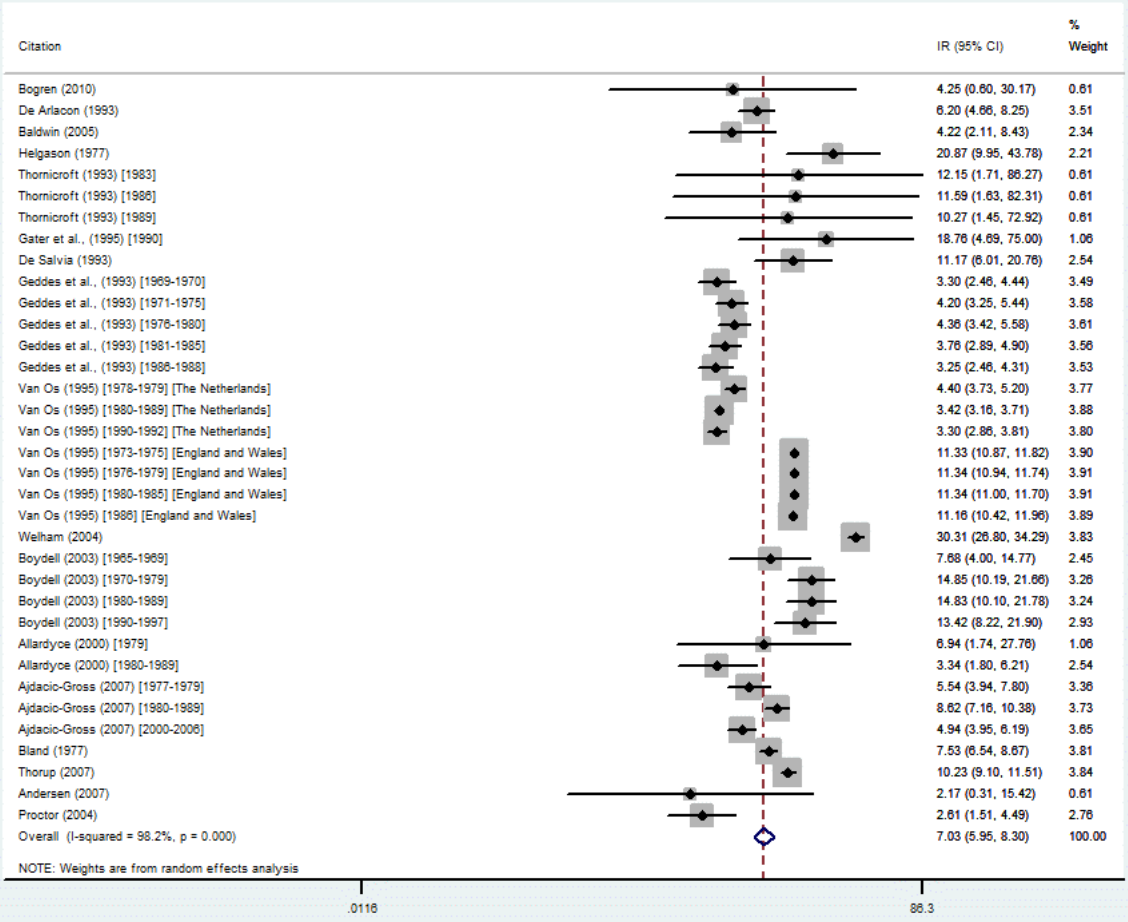
Incidence terms:
1. MeSH: Onset (disorders)
2. MeSH: Epidemiology
3. 'First episode'
4. 'First contact'
5. 'First contact admission'
6. 'First admission'
7. 'First hospitalization'
8. 'First hospitalisation'
9. Incepted
10. 'First treatment'
11. 'First treated'
12. Epidemiol*
13. Incidence
14. Cohort
15. 'Attack rate'
16. 'Inception rate'

Psychosis:
1. MeSH: Psychosis
2. Psychos*
3. Psychotic
4. Schizoaffective
5. Schizophreniform
6. Delusion*
7. Hallucinat*
8. 'Affective psychos*'
9. 'Schizophrenia-like psycho*'
10. Paranoi*
11. 'Bipolar affective psycho*'
12. 'Bipolar psycho*'
13. 'Bipolar disorder'
14. 'Psychotic depression'
15. 'Depressive psycho*'
16. 'Manic depressive psychos*'
17. 'Severe depression with psycho*'
18. Paraphrenia

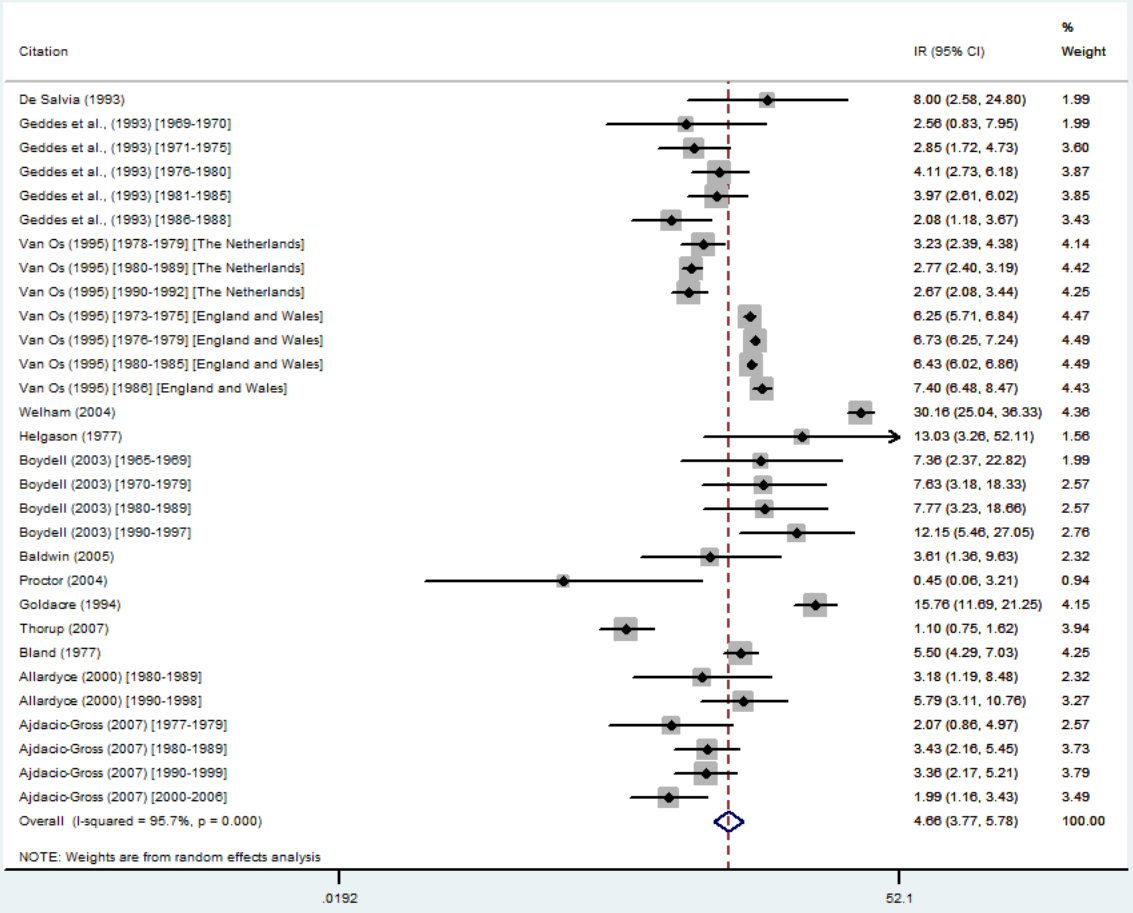
Supplementary Figure 2: Frequency of citations by year of publication



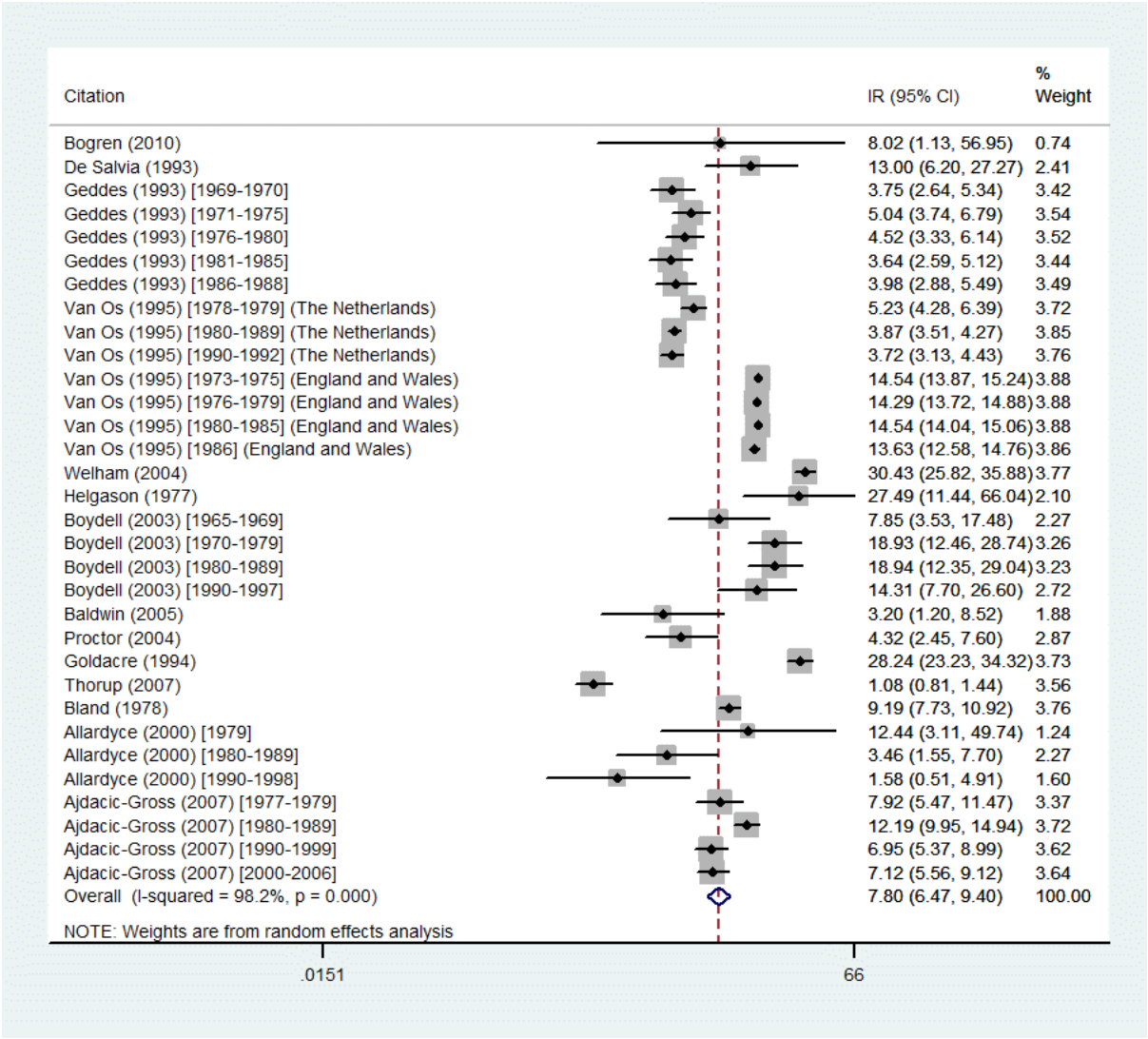
Supplementary Figure 3: Forest plot of schizophrenia incidence aged 60+ and 65+



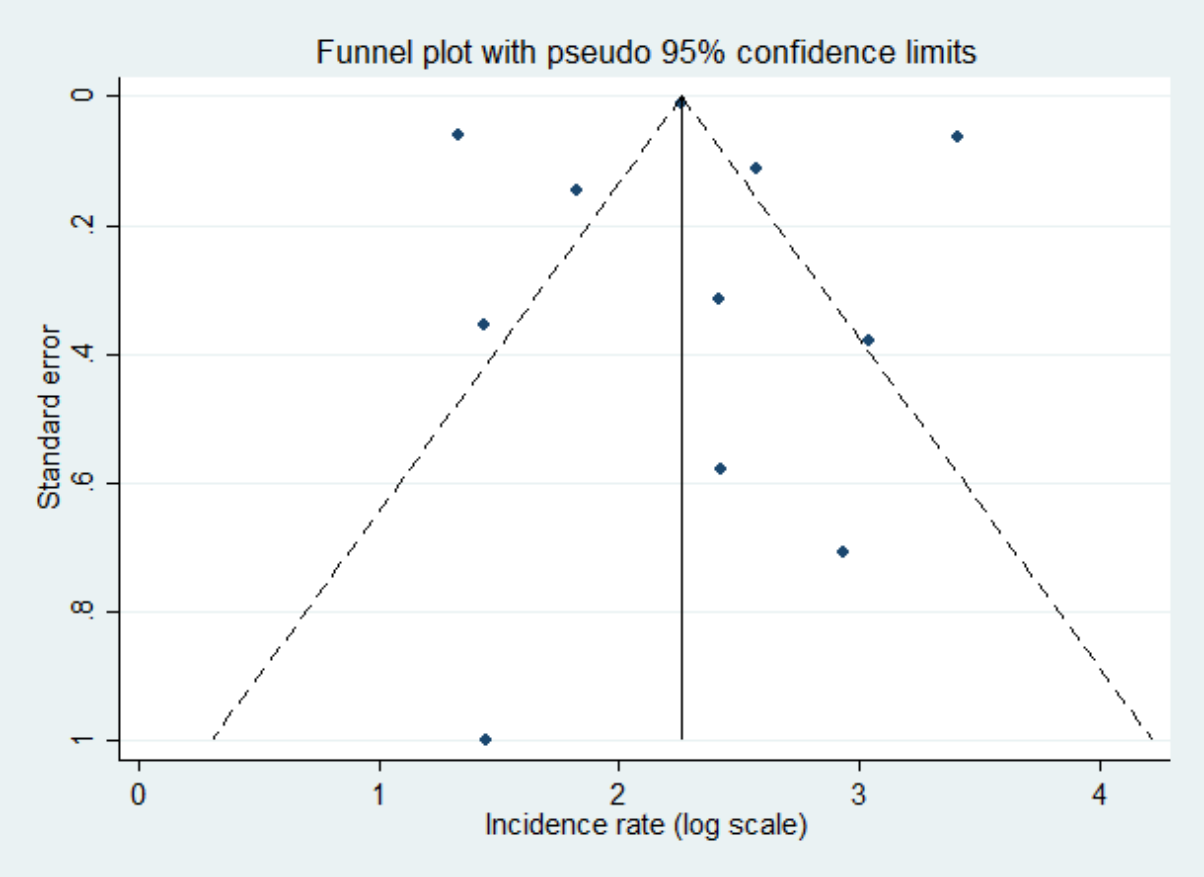
Supplementary Figure 4: Forest plot of schizophrenia incidence aged 60+ and 65+ (male)



Supplementary Figure 5: Forest plot of schizophrenia incidence aged 60+ and 65+ (female)



Supplementary Figure 6: Funnel plot of log schizophrenia incidence rates in those aged 65 and above by standard error



Supplementary Figure 7: Forest plot of affective psychosis incidence aged 65+ by sex, male (L), female (R)