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What is the duration of untreated psychosis worldwide? – A meta-analysis of pooled mean and median time and regional trends and other correlates across 369 studies

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Review Article

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Abstract

Duration of untreated psychosis (DUP) has been associated with poor mental health outcomes. We aimed to meta-analytically estimate the mean and median DUP worldwide, evaluating also the influence of several moderating factors. This PRISMA/MOOSE-compliant meta-analysis searched for non-overlapping individual studies from inception until 9/12/2022, reporting mean ± S.D. or median DUP in patients with first episode psychosis (FEP), without language restrictions. We conducted random-effect meta-analyses, stratified analyses, heterogeneity analyses, meta-regression analyses, and quality assessment (PROSPERO: CRD42020163640). From 12 461 citations, 369 studies were included. The mean DUP was 42.6 weeks (95% confidence interval (CI) 40.6–44.6, $k = 283$, $n = 41\,320$), varying significantly across continents ($p < 0.001$). DUP was (in descending order) 70.0 weeks (95% CI 51.6–88.4, $k = 11$, $n = 1508$) in Africa; 48.8 weeks (95% CI 43.8–53.9, $k = 73$, $n = 12\,223$) in Asia; 48.7 weeks (95% CI 43.0–54.4, $k = 36$, $n = 5838$) in North America; 38.6 weeks (95% CI 36.0–41.3, $k = 145$, $n = 19\,389$) in Europe; 34.9 weeks (95% CI 23.0–46.9, $k = 11$, $n = 1159$) in South America and 28.0 weeks (95% CI 20.9–35.0, $k = 6$, $n = 1203$) in Australasia. There were differences depending on the income of countries: DUP was 48.4 weeks (95% CI 43.0–48.4, $k = 58$, $n = 5635$) in middle-low income countries and 41.2 weeks (95% CI 39.0–43.4, $k = 222$, $n = 35\,685$) in high income countries. Longer DUP was significantly associated with older age ($\beta = 0.836$, $p < 0.001$), older publication year ($\beta = 0.404$, $p = 0.038$) and higher proportion of non-White FEP patients ($\beta = 0.232$, $p < 0.001$). Median DUP was 14 weeks (Interquartile range = 8.8–28.0, $k = 206$, $n = 37\,215$). In conclusion, DUP is high throughout the world, with marked variation. Efforts to identify and intervene sooner in patients with FEP, and to promote global mental health and access to early intervention services (EIS) are critical, especially in developing countries.

Introduction

Duration of untreated psychosis (DUP) is usually defined as the period between the onset of psychosis and the start of treatment for psychosis (Hegelstad et al., 2012), although other definitions have been considered (Compton et al., 2007; Golay et al., 2016). DUP has been extensively studied as a prognostic factor in psychotic disorders like schizophrenia, and longer DUP has been associated with poorer outcomes (Oliver et al., 2018; Penttila, Jaaskelainen, Hirvonen, Isohanni, & Miettunen, 2014). According to a recent umbrella review on prognostic outcomes, there is highly suggestive evidence for a relationship between longer DUP and more severe positive symptoms, negative symptoms, and lower chances of remission (Howes et al., 2021). Furthermore, there is suggestive evidence for an association between longer DUP and both poorer overall functioning and more severe global psychopathology (Howes et al., 2021).

Reducing DUP through public awareness, training, and improving treatment access should be a major goal of early intervention programs (Malla, Roy, Abdel-Baki, Conus, & McGorry, 2021). The World Health Organization and the International Early Psychosis Association produced a consensus statement 15 years ago. These organizations recommended active efforts to reduce mean DUP to less than 3 months in individuals with a first episode of psychosis (FEP) (Bertolote & McGorry, 2005). However, previous evidence has reported mean DUPs way over this threshold (61.3 weeks, $k = 33$ studies, non-metanalytical evidence) (Penttila et al., 2014). The DUP distribution is usually right-skewed, as there are some individuals with very long

DUP, which are challenging to detect and engage in treatment with current strategies (Johannessen et al., 2001). Thus, the median DUP is generally lower than the mean DUP (12 weeks, according to evidence from 28 studies) (Boonstra et al., 2012). Currently, the efficacy of interventions to reduce DUP is limited (Oliver et al., 2018). It is further insufficiently clear, which factors result in a longer or a shorter DUP, including variations across different continents, which may be related to different pathways to care, including the availability and use of early intervention services (EIS). Moreover, multiple demographic factors can influence DUP, and a better understanding of the relationship between such factors and DUP is critical to inform resource planning and allocation that would improve strategies to detect and treat patients early in the course of their psychotic illness.

While a recent meta-analysis estimated the association between DUP and outcomes both at baseline and follow-up (Howes et al., 2021), to the best of our knowledge, no study has quantified meta-analytically the duration of untreated psychosis and its correlates. A plethora of studies reporting on the duration of DUP and potential correlates have been published, making an evaluation of the DUP characteristics and correlates worldwide essential, particularly to review if and where the desired or even targeted reduction of DUP has been achieved. Thus, the aim of this study was to meta-analytically evaluate the mean and median DUP worldwide and in each continent, evaluating also for the first time a wide range of factors that may moderate DUP.

Methods

This meta-analysis (PROSPERO:CRD42020163640) was conducted in accordance with the guidelines of the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA, eTable I) (Moher, Liberati, Tetzlaff, & Altman, 2009) and the 'Meta-analyses Of Observational Studies in Epidemiology' (Moose) checklist (eTable II) (Stroup et al., 2000).

Search strategy and selection criteria

A systematic search strategy was used to identify relevant articles, and independent researchers implemented a two-step literature search. The following search terms were applied: ('schizophrenia' OR 'schizoaffective' OR 'schizophreniform' OR 'psychosis' OR 'psychotic') AND ('first episode' OR 'early episode' OR 'early phase' OR 'first break' OR 'duration untreated psychosis'). First, independent researchers conducted the electronic search in PubMed, PsychInfo, SciElo Citation Index and KCI Korean Journal databases from inception until 1 November 2020, without restrictions on language. The literature search was subsequently updated up to 08 December 2022. Titles and abstracts of articles identified were screened, and after the exclusion of those which did not meet our inclusion criteria, the full texts of the remaining articles were assessed for eligibility. Then, final decisions were made regarding their inclusion in the review by consensus or remediation by the first and/or last author. We completed our search by manually reviewing the references of the included articles. The following inclusion criteria were used to select the articles: (a) individual studies, (b) conducted in FEP, either with affective psychosis, non-affective psychosis or both, (c) reporting either mean ± S.D. DUP and/or median DUP (see eMethods I for DUP operationalization), (d) in any language, and (e) without restrictions on sex, age, or ethnicity. Exclusion criteria were the following: (a) reviews, clinical cases, abstracts, and study protocols, (b) studies reporting DUP using other measures or evaluating DUP categorically (i.e. not reporting mean ± S.D. or median DUP), (c) overlapping studies as defined by study program and recruitment period as well as ⩾50% overlap in recruitment periods (>50 authors were contacted for missing data or clarify overlap).

Outcome measures and data extraction

Data were independently extracted by consultant psychiatrists/senior clinical academics. Any discrepancies were resolved through consensus meetings, or consulting the first and/or last authors. The variables extracted included: first author and year of publication, country, design (cross-sectional *v.* longitudinal *v.* clinical trial), sample size, mean age, sex (% males), FEP diagnosis (structured *v.* clinical), DUP definition (see eMethods I and operationalization below), substance use disorders (included *v.* excluded), affective psychosis (included *v.* excluded, and % affective psychosis), % white race, % single, % married, % living alone, main outcome (mean ± S.D. DUP, median DUP or both, in weeks), and quality (see below).

Operationalization duration of untreated psychosis

DUP is typically operationalized as the period between the onset of psychotic symptoms and the initiation of intervention (Howes et al., 2021). The initiation of intervention may be defined according to the establishment of the first antipsychotic medication (Rizos et al., 2010), the first contact with a mental health care provider (Johnstone, Crow, Johnson, & MacMillan, 1986) or the first hospitalization (Jonas et al., 2020). Other definitions have been piloted. Some studies use instead of the first psychotic symptom the first psychiatric symptom (Compton et al., 2007), the first changes in behavior (Marchira, Supriyanto, Subandi, Soewadi, & Good, 2016) or the prodromal period (Beiser, Erickson, Fleming, & Iacono, 1993) as the starting point. The first effective treatment (Polari et al., 2011) and the first treatment for which adherence has been achieved (Casey et al., 2016) have been used as an alternative end point of DUP. Different instruments have been considered to operationalize DUP, including the 'Circumstances of Onset and Relapse Schedule' (CORS) (Malla et al., 2006); the 'Interview for the Retrospective Assessment of the Onset of Schizophrenia' (IRAOS) (Häfner et al., 1992); the 'Nottingham Onset Schedule' (NOS) (Singh et al., 2005); and the 'Beiser scale' (Beiser et al., 1993).

Strategy for data synthesis

We first provided a quantitative summary of the DUP worldwide for studies providing mean ± S.D. (in weeks), which was the primary outcome of this meta-analysis. Data from studies providing DUP values in another time measure (i.e. days/months/years) were converted to weeks. When mean ± S.D. DUP was reported for the subgroups only (i.e. when the results for the total FEP were unavailable), subgroup information was combined weighted by sample size, using a calculator developed in an excel file. Furthermore, we extracted the median, interquartile range (IQR) and range of the DUP for the studies reporting median DUP. When the studies reported median DUP for the subgroups only, and when overall results from the authors to see the distribution of the whole sample could not be obtained, data from the subgroups were introduced independently since it was not

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possible to precisely estimate the overall median DUP without knowing the data distribution.

Since high heterogeneity was expected, random-effects meta-analyses were conducted (DerSimonian & Laird, 1986). Heterogeneity among study point estimates was assessed using the Q statistics and Tau^2. The proportion of the total variability in the effect size estimates was evaluated with the I^2 index (i.e. $I^2 < 50\%$: non-significant heterogeneity, $I^2 \geqslant 50$–74%: moderate heterogeneity, $I^2 \geqslant 75\%$: marked heterogeneity) (Lipsey & Wilson, 2000). Publication bias was assessed by visually inspecting the funnel plot and by conducting Egger's test (Egger, Davey Smith, Schneider, & Minder, 1997). Prediction intervals were further calculated.

Multiple sub-analyses were conducted for both mean and median DUP. Stratified DUP was estimated when three or more studies were available per predefined subgroup. Sensitivity analysis included stratified mean and median DUP results according to (i) publication decade (1991–2000 *v.* 2001–2010 *v.* 2011–2020 *v.* 2021–2022), (ii) study continent (Europe *v.* Asia *v.* Africa *v.* North America *v.* South America *v.* Australasia), (iii) income level (high income countries *v.* middle-low income countries) (as defined by the World Bank country classifications by income level (2022–2023)) (iv) FEP diagnosis (structured *v.* clinical), (v) DUP definition (from first psychotic symptom to antipsychotic treatment intervention *v.* other definitions, see eMethods I), (vi) exclusion *v.* lack of exclusion of FEP with substance use disorders, (vii) samples with only non-affective psychosis *v.* samples where FEP with affective psychosis were included, (viii) exclusion long DUP (DUP over a threshold -as per author's definition- excluded *v.* long DUP not excluded/ not mentioned) and (ix) setting (samples from FEP programs *v.* others). Sensitivity analyses according to publication decade by study continent for those continents with enough number of studies (Europe, Asia, North America) were also carried out. Sensitivity analyses for countries with at least 10 independent samples were carried out.

To compare subgroups for the median DUP, since a meta-analysis would not accurately reflect the distribution of the differences in medians, non-parametric individual analyses (Kruskal–Wallis) were used to evaluate subgroup differences using https://www.socscistatistics.com/tests/kruskal/default.aspx, and H statistic and p values were provided. Finally, for the studies providing both mean ± S.D. and median ± IQR DUP metrics, a meta-analysis was conducted to directly compare mean and median DUP values from in the same population assessed with the same definition of DUP. For this analysis, the width of the IQR was considered as 1.35 S.D.s (https://handbook-5-1.cochrane.org/chapter_7/7_7_3_5_mediansand_interquartile_ranges.htm), following Cochrane's guidelines. These two last sensitivity analyses were not part of the initial protocol.

Furthermore, we conducted meta-analytic regression analyses for our primary outcome (mean DUP) whenever ten or more studies were available (Cumpston et al., 2019) to estimate the association between the mean DUP and the (i) % with affective psychosis, (ii) mean age, (iii) sex (% males), (iv) sample size, (v) year of publication, (vi) % white race, (vii) % single, (viii) % married, (ix) % living alone, and (x) quality of the study (total NOS score). https://mapchart.net/world-advanced.html was used to create a figure with the countries in which DUP was reported in at least one of the included studies. Comprehensive Meta-analysis (CMA) V3 (Borenstein, Hedges, Higgins, & Rothstein, 2013) and Stata statistical software version 16 (StataCorp) (Nyaga, Arbyn, & Aerts, 2014) were used to perform the analyses that were all two-sided and with alpha = 0.05.

Risk of bias (quality) assessment

Study quality was assessed using items from the Newcastle-Ottawa Scale for cohort studies (Wells et al., 2014). A score of 0–9 was reported based on representativeness, selection of the cohorts, ascertainment of exposure, outcome of interest, comparability of cohorts, assessment of outcomes, and duration/adequacy of follow-up (see eMethods II).

Results

Sample characteristics

The literature search yielded 12 461 citations, which were screened for eligibility, 3359 full-text articles were assessed and 369 studies were included in the meta-analysis (Fig. 1): 283 studies reporting mean ± S.D. DUP and 206 reporting median DUP (i.e. some studies reported only mean ± S.D. or median DUP while others reported both measures). The database included 57 715 FEP individuals. The sample size ranged from 7 to 1724 FEP individuals (eTable III). The mean age was 26.1 ± 4.5 and ranged 14.7–45.5 years. The proportion of males in the included studies was 62.0% and the years of education 11.2 ± 3.0. Altogether, 43.7% were white, 75.4% were single, 17.2% were married, and 22.8% were living alone (eTable III).

Quality assessment

Study quality scores ranged from 3 to 9 (eTable III). The overall mean quality score of the included studies was 6.6 ± 1.4.

Duration of Untreated Psychosis worldwide and by continents

The pooled mean DUP was 42.6 weeks (95% CI 40.6–44.6, $k = 283$; $n = 41\,320$). Differences were found between the studies according to the continent in which the study was carried out ($Q = 42.7$, $p < 0.001$). DUP ranged (in descending order) from 70.0 weeks (95% CI 51.6–88.4, $k = 11$; $n = 1508$) in Africa; 48.8 weeks (95% CI 43.8–53.9, $k = 73$; $n = 12\,223$) in Asia; 48.7 weeks (95% CI 43.0–54.4, $k = 36$; $n = 5838$) in North America; 38.6 weeks (95% CI 36.0–41.3, $k = 145$; $n = 19\,389$) in Europe; 34.9 weeks (95% CI 23.0–46.9, $k = 11$; $n = 1159$) in South America and to 28.0 weeks (95% CI 20.9–35.0, $k = 6$; $n = 1203$) in Australasia (Table 1, eTable IV-A). In Europe, mean DUP ranged from 88.0 weeks (95% CI 18.5–157.6) in the 1991–2000 decade; 39.0 weeks (95% CI 34.4–43.6) in the 2001–2010 decade, 42.5 weeks (95% CI 38.6–46.4) in the 2011–2020 decade, and to 23.8 weeks (95% CI 18.2–29.3) in the 2021–2022 decade, with differences according to the publication decade being statistically significant in Europe ($Q = 32.3$, $p = <0.001$), but not the other continents with sufficient data (Asia: $p = 0.574$; North America: $p = 0.524$) (eTable IV-B).

The pooled median DUP was 14 weeks (Interquartile range [IQR] 8.8–28.0, $k = 206$; $n = 37\,215$): DUP in the studies conducted in different continents varied ($H = 9.5$, $p = 0.049$), ranging (in descending order) from 22.5 weeks in Africa (IQR = 6.0–47.7, $k = 10$; $n = 1211$); 20.8 weeks in North America (IQR 9.1–35, $k = 37$; $n = 7390$); 17.1 weeks in Asia (IQR = 12–28.9, $k = 43$; $n = 8689$); 12.0 weeks in Europe (IQR = 8.2–27, $k = 102$; $n = 16\,500$); 10 weeks in South America (IQR = 8.7–14, $k = 6$; $n = 1055$) and to 8 weeks in Australasia (IQR = 6.0–13.0, $k = 8$; $n = 2370$). No other subgroup differences were found according to the continent where the study was conducted, FEP diagnosis or exclusion of substance use disorders or affective psychosis (Table 2, eTable V).

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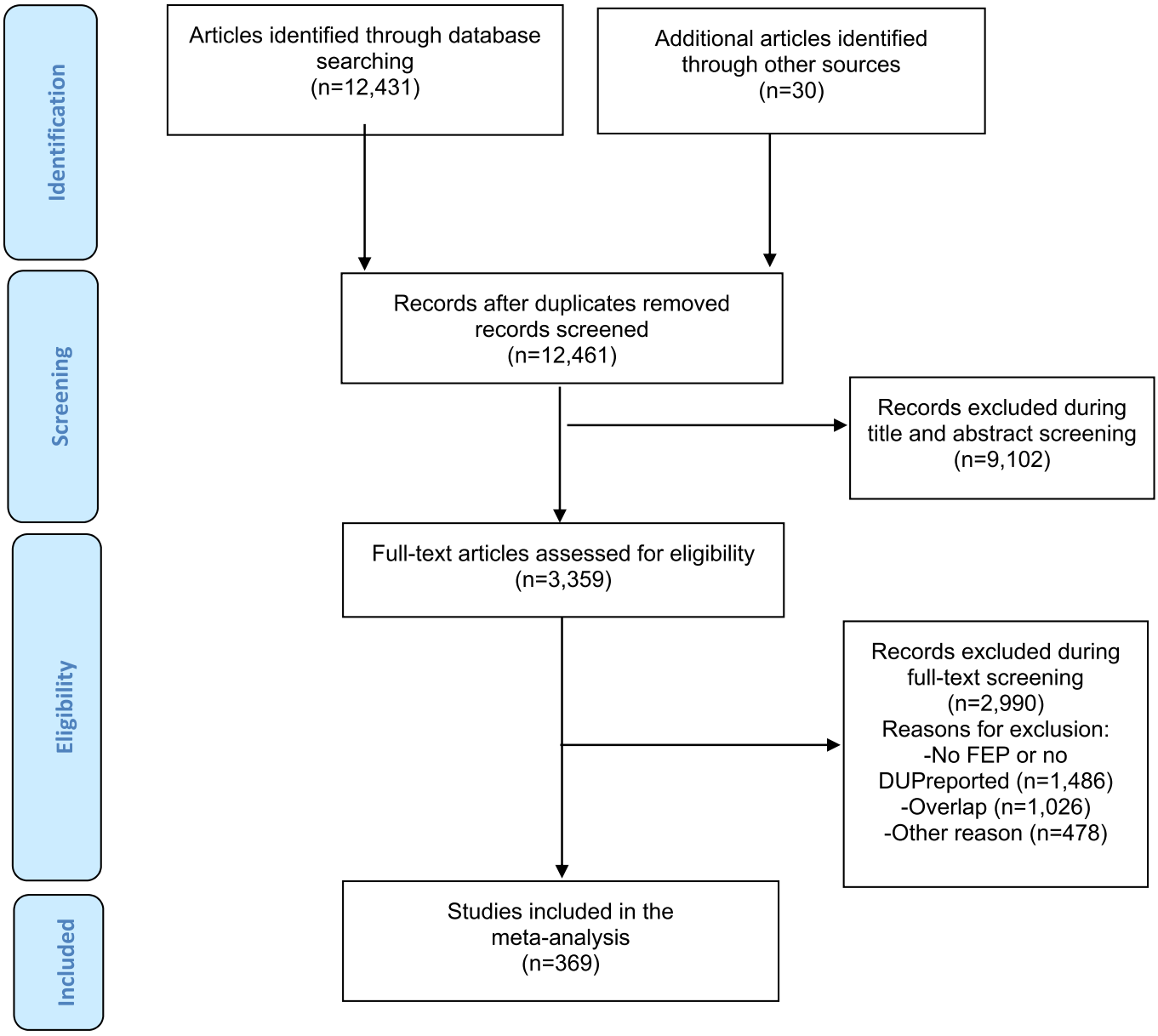

Figure 1. PRISMA flow diagram.

Table 1. Meta-analysis mean duration of untreated psychosis (in weeks)

Group, subgroup	No. of Studies	Sample size	DUP (in weeks)			Z score	p	Test for heterogeneity				Prediction interval
			Mean	95% CI				Q	I^2	Tau^2	P	
Overall	283	41 320	42.6	40.6	44.6	41.4	<0.001	12 713.3	97.8	229.2	<0.001	12.1–73.1
Africa	11	1508	70.0	51.6	88.4	7.5	<0.001	237.7	95.8	219.2	<0.001	8.0–132.0
Asia	73	12 223	48.8	43.8	53.9	18.9	<0.001	4042.9	98.2	407.8	<0.001	6.9–90.7
North America	36	5838	48.7	43.0	54.4	16.7	<0.001	992.5	96.5	832.8	<0.001	37.9–59.5
Europe	145	19 389	38.6	36.0	41.3	28.4	<0.001	7085.5	98.0	205.2	<0.001	10.3–66.9
South America	11	1159	34.9	23.0	46.9	5.7	<0.001	89.7	94.4	100.4	<0.001	2.1–67.7
Australia	6	1203	28.0	20.9	35.0	7.7	<0.001	83.9	88.1	94.4	<0.001	2.4–53.6

DUP, duration of untreated psychosis.

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Table 2. Meta-analysis median duration of untreated psychosis (weeks)

			DUP in weeks			
Group, subgroup	No. of Studies	Sample size	Median	IQR		Range
Overall[a]	206	37 215	14	8.8	28.0	0.6–110
Africa	10	1211	22.5	6.0	47.7	6–110
North America	37	7390	20.8	9.1	35	0.6–52.1
Asia	43	8689	17.1	12	28.9	1.7–52
Europe	102	16 500	12	8.2	27	0.7–104
South America	6	1055	10	8.7	14	4.0–28
Australia	8	2370	8	6.0	13	4.3–40.8

DUP, duration of untreated psychosis; IQR: Interquartile range.
[a]Between group heterogeneity was observed (H = 9.5, $p = 0.049$).

Stratified analysis of duration of untreated psychosis

The mean DUP ranged between 58.5 weeks (95% CI 33.4–83.5; $k = 5$; $n = 286$) in the 1991–2000 decade; 42.8 weeks (95% CI 39.1–46.6; $k = 62$; $n = 8889$) in the 2001–2010 decade, 44.5 weeks (95% CI 41.6–47.4; $k = 169$; $n = 25\,835$) in the 2011–2020 decade, and 35.4 weeks (95% CI 31.1–39.7; $k = 47$; $n = 6664$) in the 2021–2022 decade, with significant differences across decades (Q 13.9, $p = 0.003$ eTable IV-A). DUP differed depending on the income level of countries where the studies were conducted, with longer DUP in middle-low than in high-income countries (48.4 weeks, 95% CI 43.0–48.4; $k = 58$; $n = 5635$ *v.* 41.2 weeks, 95% CI 39.0–43.4; $k = 222$; $n = 35\,685$), $Q = 5.8$, $p = 0.016$). DUP was shorter in studies excluding individuals with DUP over a threshold (23.4 weeks, 95% CI 11.9–35.6; $k = 7$, $n = 920$) compared to those not excluding them (43.0 weeks, 95% CI 40.9–45.0; $k = 276$, $n = 40\,757$) ($Q = 13.8$, $p = 0.001$). The median DUP ranged between 16 weeks (IQR = 8.0–18, $k = 6$; $n = 541$) in the 1991–2000 decade; 13 weeks (IQR = 8.4–26, $k = 63$; $n = 11\,383$) in the 2001–2010 decade; 15.5 weeks (IQR = 8.7–32.7, $k = 130$; $n = 24\,662$) in the 2011–2020 decade; and 11 weeks (IQR = 8.6–21.7, $k = 7$; $n = 629$) in the 2021–2022 decade (eTable V).

The meta-analytic mean and median DUP for the 43 independent studies providing both metrics was 44.2 weeks (95% CI 39.4–49.0) for mean DUP and 17.4 weeks (95% CI 14.5–20.3) for median DUP. Among the countries with at least ten studies available, mean DUP ranged from 27.5 weeks in Spain (95% CI 22.0–33.0, $k = 23$; $n = 3063$) to 50.6 weeks in Japan (95% CI 40.8–60.4, $k = 17$; $n = 1447$).

Studies in which FEP with affective psychosis were excluded had a higher mean DUP (46.7 weeks, 95% CI 44.0–49.4, $k = 168$; $n = 18\,212$) compared to studies including individuals with affective psychosis (37.7 weeks, 95% CI 34.2–41.1, $k = 96$; $n = 18\,086$) ($Q = 16.7$, $p < 0.001$). No differences in DUP were found according to the DUP definition, the exclusion of FEP with substance use disorders, the use of structured or clinical instruments to diagnose FEP or the setting (all $p > 0.05$) (eTable IV-A). Stratified analyses for median DUP can be seen at eTable V.

Heterogeneity and publication bias assessment

Heterogeneity was marked for the primary analysis evaluating mean DUP ($I^2 = 97.8\%$, $Q = 12\,713.3$, $p < 0.001$, $\text{Tau}^2 = 229.2$), as well as for the stratified analysis by study continent ($I^2 = 88.1$–98.2%, $Q = 83.9$–7085.5, $\text{Tau}^2 = 94.4$–832.8, all $p < 0.001$). Publication bias was not identified.

Meta-regression analyses

Longer DUP was associated with older mean patient age ($\beta = 0.836$, $p < 0.001$), older year of publication ($\beta = 0.404$, $p = 0.038$) and higher proportion of non-White FEP patients ($\beta = 0.232$, $p < 0.001$) (Table 3). No significant associations were found

Table 3. Meta-regression analyses

	No. of Studies	β Coefficient	s.e.	95% CI		Z Value	p value
% Affective psychosis	235	−0.130	0.119	−0.362	0.103	−1.09	0.275
Mean age	**266**	**0.836**	**0.250**	**0.346**	**1.325**	**3.35**	**<0.001**
% males	274	−0.051	0.029	−0.108	0.0067	−1.73	0.083
Sample size	280	0.051	0.004	−0.004	0.014	1.13	0.260
Year of publication	**280**	**−0.404**	**0.195**	**−0.786**	**−0.022**	**−2.07**	**0.038**
% White race	**64**	**−0.232**	**0.055**	**−0.339**	**−0.125**	**−4.26**	**<0.001**
% Single	29	−0.006	0.216	−0.430	0.417	−0.03	0.977
% Married	24	−0.0011	0.360	−0.706	0.704	0.00	0.997
% Living Alone	21	−3.296	1.807	−6.827	0.256	−1.82	0.069
Quality of the study	280	1.211	0.754	−0.267	2.689	1.610	0.108

Bold means $p < 0.05$.

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between DUP and the % of affective psychosis, sample size, % of males, % of single/married individuals, % of those living alone or quality of the studies (all $p > 0.05$).

Discussion

To our knowledge, with 359 studies (283 studies reporting mean ± S.D. DUP; 206 reporting median DUP) and 57 715 FEP individuals, this is the largest meta-analysis to summarize the mean and median DUP worldwide. We further evaluated comprehensively, for the first time, the influence of a broad range of moderating factors through our stratified subgroup and meta-regression analyses.

The pooled mean DUP was 42.6 weeks (95% CI 40.6–44.6) and the pooled median DUP was 14 weeks (IQR 8.8–28.0) in FEP individuals. Thus, the recommendations established over 15 years ago of reducing mean DUP to less than 3 months in individuals with a FEP (Bertolote & McGorry, 2005) have not been implemented successfully with the current strategies. The 300% longer mean DUP than median DUP indicates that a significant subgroup of patients has a very long DUP, right-skewing the results of the mean. Information about this subgroup and how to reach and engage these FEP patients in treatment earlier is at least as important as reducing the DUP in all individuals where it is longer than 3 months. Future studies should report DUP and characteristics by group tertiles, quartiles or quintiles (depending on sample size) to advance the discussion about targeted interventions to reduce the DUP and whether a reduction in DUP would improve outcomes.

Differences in DUP duration were observed according to the publication decade – although not for median DUP -, indicating some overall reduction in the mean DUP worldwide over time and compared to previous evidence from the first 33 published studies (42.6 *v.* 61.3 weeks [Penttila et al., 2014]). However, the pooled median DUP remained somewhat higher than the previous meta-analytically pooled evidence [14 *v.* 12 weeks (Boonstra et al., 2012)]. The most likely interpretation is that there are still individuals with very long DUP who are challenging to detect and thus are less likely to receive appropriate early interventions at the moment (Johannessen et al., 2001). Unsurprisingly, in our sub-analyses, when authors excluded individuals with long DUP from their studies, the DUP decreased, which supports this hypothesis. In any case, delays in access to clinical care/appropriate care have remained frequent, which highlights an urgent need to improve current early intervention strategies for those individuals with FEP who are particularly difficult to detect early in their course of their psychotic illness (Lloyd-Evans et al., 2011; Perkins, Gu, Boteva, & Lieberman, 2005).

The DUP varied across continents, and some continents were more represented than others in this meta-analysis. At the same time, the DUP from some regions and countries has never been reported or at least published in peer-reviewed journals (see Fig. 2). DUP was almost triple in Africa (mean DUP = 70.0 weeks, median DUP = 22.5 weeks) than in Australia (mean DUP = 28.0 weeks, median DUP = 8 weeks); a possible explanation for this is a lack of resources, particularly for early intervention across most of Africa, contrasted by the publicly-funded presence of a longstanding tradition to implement EIS in Australia (Malla & McGorry, 2019) where mean and median DUP was lower than on any other continent. Thus, these results suggest that countries such as Australia, pioneering the EIS programs, have been able to manage the earlier detection and treatment of patients with FEP more successfully than other regions in the world that should learn from the Australian model, supported

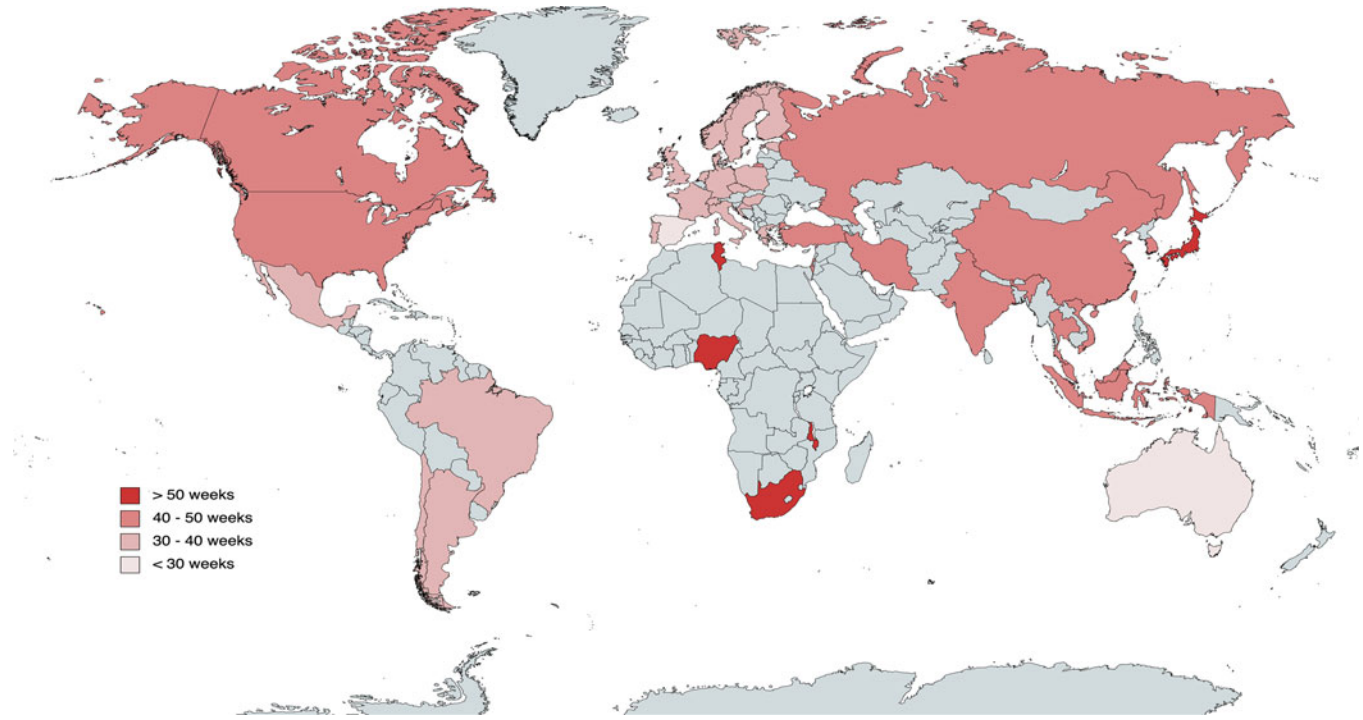

Figure 2. MAP with countries worldwide reporting mean DUP*.
*The DUP for countries with at least 10 independent samples was individually calculated. The rest are represented according to the meta-analytical results in their continent.

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by public funding. Equally DUP was longer in middle-low income countries compared to high income countries.

In our meta-regression analyses, White ethnicity was associated with shorter DUP, which is worrying, as it highlights difficulties to access clinical services by ethnic minorities. Furthermore, this finding suggests that differential pathways to care may not only exist across different geographical locations but also within the same region, and that social determinants of heath, including elements of culture, health literacy, stigma, social stress and exclusion, health access, and inequality require focused attention (Filia et al., 2022; Guinart, Kane, & Correll, 2019; Rice, Purcell, & McGorry, 2018; Salazar de Pablo et al., 2020). In fact, within the same population in Canada, the median DUP was more than double in Black-Caribbean individuals than in White-Europeans (Anderson et al., 2015). Furthermore, rates of schizophrenia were found to be higher in Black Caribbean (RR: 5.6), Black African (RR: 4.7) and South Asian individuals (RR: 2.4) compared to White British individuals in the UK (Kirkbride et al., 2012). Black, Asian, mixed, and other ethnicities have been associated with an increased risk of developing psychosis relative to White ethnicity, and are used in risk calculators to predict psychosis onset (Fusar-Poli et al., 2017b). Our results highlight the importance of launching culturally sensitive global health and global mental health programs and campaigns to better detect the specific needs and to identify and treat ethnic minority groups earlier. Global health intends to improve health and achieve equity in health for all people worldwide (Koplan et al., 2009; Patel & Prince, 2010). Global mental health and promotion of mental health to achieve the same goals are equally important (Salazar de Pablo et al., 2020). However, significant barriers to service delivery in global mental health exist, including lack of culturally appropriate screening tools and interventions and human resources trained to deliver the necessary care (Qureshi et al., 2021). Future research and health governance should advance by developing culturally sensitive approaches (Snodgrass, Lacy, & Upadhyay, 2017).

EIS typically provide treatment and support for both individuals experiencing psychosis and individuals who are at clinical high-risk of developing psychosis (CHR-P) (NHS-England The National Collaborating Centre for Mental Health and the National Institute for Health and Care Excellence, 2016). The CHR-P paradigm originated in Australia 25 years ago (Yung et al., 2005). Australia is known for its mental health initiatives for young people (Rickwood et al., 2019), including services for individuals at CHR-P and EIS, which according to our results appear to have been more capable than other regions to yield a lower DUP. Implementing CHR-P services have been considered the most effective method for lowering DUP (Oliver et al., 2018), since individuals can receive preventive interventions before they transition to psychosis. Furthermore, the detection of individuals at CHR-P (Fusar-Poli, Sullivan, Shah, & Uhlhaas, 2019) and the development and implementation of preventive interventions (Fusar-Poli et al., 2020) can maximize the benefits of early intervention in people at risk for and with psychosis (Correll et al., 2018; Fusar-Poli, McGorry, & Kane, 2017a). However, currently, only a small proportion of individuals with manifest FEP had been previously seen at CHR-P services (Ajnakina et al., 2017). Therefore, additional strategies to reduce DUP effectively both across patients with FEP and within subgroups of greatest need to reduce the DUP are needed. So far, we did not detect a reduction in DUP in those studies reporting results from a FEP program compared to other studies. It may also be that our statistical power was limited ($K = 35$ studies in the FEP group). In any case, meta-analytical evidence from randomized clinical trials may be able to better clarify whether FEP services focusing on DUP result in a decrease in DUP.

According to our meta-regression analyses, besides a larger proportion of non-White individuals, discussed above, a higher mean age was also associated with a longer DUP. One hypothesis why higher mean age might be associated with longer DUP is that it may be particularly challenging for older individuals to access clinical care (Mikton, de la Fuente-Núñez, Officer, & Krug, 2021). Most EIS for FEP only accept patients until 35 years (Grawe, Falloon, Widen, & Skogvoll, 2006) or 40 years (Kane et al., 2016). Furthermore, 85.7% of CHR-P services only accept individuals until 35 years (Salazar de Pablo, Estradé, Cutroni, Andlauer, & Fusar-Poli, 2021), and some have even younger thresholds (Tiffin & Hudson, 2007) or only accept individuals within 2 years of psychosis onset (Dixon, Goldman, Srihari, & Kane, 2018). The age of onset may also be similar and the older age in individuals with longer DUP may be an artifact or a consequence of DUP *per se*. These considerations may suggest age and gender-sensitive approaches in early psychosis programs (Sommer, Tiihonen, van Mourik, Tanskanen, & Taipale, 2020). Additionally, younger individuals with FEP may still be embedded and engage in more social contexts, which may increase surveillance and identification of problems, leading to the initiation of mental help seeking behaviors.

Interventions to reduce DUP based on early detection and intervention have been developed in FEP (Correll et al., 2018; Lieberman, Small, & Girgis, 2019). A previous meta-analysis found that EIS were superior to treatment as usual on a wide range of clinical and functional outcomes (Correll et al., 2018). Benefits of EIS may include a decrease of suicide attempts (Chan et al., 2018; Melle et al., 2010) and an increase of service users' satisfaction as well (Cullberg, Levander, Holmqvist, Mattsson, & Wieselgren, 2002). From a management perspective, the costs of EIS are lower than the control group costs (Mihalopoulos, Harris, Henry, Harrigan, & McGorry, 2009), particularly due to lower inpatient costs (Cullberg et al., 2006). Unfortunately, the capacity of EIS for reducing DUP has been limited (Oliver et al., 2018). There is still a significant subgroup of individuals with very long DUP (Johannessen et al., 2001), that can only reach care with intensive efforts from professionals and outreach strategies (Lynch et al., 2016) including information campaigns (Joa et al., 2008) as well as social media and digital approaches (Birnbaum et al., 2018; Birnbaum, Rizvi, Confino, Correll, & Kane, 2017). Barriers to early detection include difficulties to detect signs of early psychosis (Lloyd-Evans et al., 2015), worries about stigma or coercive treatment (Lloyd-Evans et al., 2015), and family difficulties (Qiu et al., 2019). The influence of other clinical and social factors should be considered and addressed. For instance, meta-analytic evidence found a significant association between cannabis use and a 2.7 years earlier age at the onset of psychosis (Large, Sharma, Compton, Slade, & Nielssen, 2011), which is a relevant consideration given the multinational developments towards legalization of cannabis use (Pearson, 2019).

The current study has several limitations. First, despite the large overall database, the number of studies was limited for some of the subgroups. For instance, the number of studies providing data on DUP in Africa, South America or Australia was more limited than the number of studies providing DUP results in Europe or Asia, and there was no information available for

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some countries. Furthermore, there were only five studies published in the 1991–2000 decade, in part because some of the cohorts and programs established in that decade published more extensive but significantly overlapping results in later years, which we had to exclude to avoid double-counting. However, the database was large and sufficiently powered to test our hypothesis. Second, heterogeneity was significant for DUP, and thus prediction intervals are broad. Different factors may have influenced the results. We conducted additional meta-regression and subgroup analyses to evaluate the influence of some of these factors. This heterogeneity of the results is common in real-world scenarios, which may have helped us obtain a broader, more realistic picture of the current state of the field. Third, the definitions of DUP were heterogeneous, and 148 studies (40%) did not provide a definition for DUP. Lack of differences in DUP results depending on the definition may have been influenced by this lack of information or lack of statistical power. Alternatively, variations in DUP due to differences in its definition may simply be too small compared to the many other, more powerful factors prolonging DUP. Fourth, only 6.5% of FEP individuals had affective psychosis, while higher proportions have been reported in the literature. Future research should disentangle the peculiarities of individuals with affective psychosis regarding DUP compared to individuals with non-affective psychosis. Fifth, the observed correlation between older age and longer DUP could well be due to the correlated nature of the two variables. Future studies should explore the correlations within birth/age cohorts, ideally using individual level data, in order to better examine this feature. Sixth, the results for the median DUP were not meta-analytical but calculated based on the distributions as advised by expert statisticians. Finally, we did not evaluate the impact of DUP or its consistency as a prognostic factor for the illness trajectory or as a predictive factor for either the effect of the clinical interventions to reduce DUP or for DUP as a moderator of treatment for FEP. These topics have previously been addressed elsewhere (Howes et al., 2021) and will need to be reviewed periodically in future studies and meta-analyses.

In conclusion, DUP remains problematically high throughout the world, and particularly so in some less developed continents. Although mean DUP has been reducing globally, it remains longer than recommendations, even in regions with a strong public health focus on early identification and intervention. This highlights the need for further efforts to intervene sooner and to promote global mental health and access to early intervention, particularly in developing countries. EIS should pay greater attention to the earlier and culturally sensitive detection and intervention of ethnic minority groups, and limiting the age or illness duration as criteria for inclusion might need to be reconsidered, given the particularly long DUP in older individuals who will otherwise be excluded albeit requiring increased attention.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003458

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Competing interests. Dr Salazar de Pablo has received honoraria from Janssen Cilag and Menarini. Dr Aymerich has received honoraria from Neuraxpharm. Dr Guinart has been a consultant for and/or has received speaker honoraria from Angelini, Janssen, Lundbeck, Otsuka, Teva, Viatris. Dr Rubio has received consulting fees from TEVA, Janssen and Karuna, research support from Alkermes, royalties from UpToDate. Prof Howes is a part-time employee and stock holder of Lundbeck A/s. He has received investigator-initiated research funding from and/or participated in advisory/ speaker meetings organized by Angellini, Autifony, Biogen, Boehringer-Ingelheim, Eli Lilly, Heptares, Global Medical Education, Invicro, Jansenn, Lundbeck, Neurocrine, Otsuka, Sunovion, Recordati, Roche and Viatris/ Mylan. Dr Howes has a patent for the use of dopaminergic imaging. Dr Kane has been a consultant and/or advisor to or has received honoraria from: Acadia, Alkermes, Allergan, Biogen, Boehringer-Ingelheim, Cerevel, Click, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, Merck, Neurocrine, Newron, Otsuka, Reviva, Saladax, Sunovion and Teva. He has received grant support from Lundbeck, Otsuka, Janssen and Sunovion. He is a shareholder of HealthRhythms, LB Pharma, Medincell and The Vanguard Research Group. Dr Fusar-Poli has received research fees from Lundbeck and honoraria from Lundbeck, Angelini, Menarini and Boehringer Ingelheim outside the current study. Prof Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Mindpax, LB Pharma and Quantic.

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