




The differential impact of duration of untreated psychosis on functioning and quality of life: A threshold analysis

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Abstract

Aim: Reduction of duration of untreated psychosis (DUP) remains a key goal of early intervention programs. While a significant body of literature suggests that a short DUP has a positive impact on outcome, little is known regarding the threshold above which various dimensions of outcome are impaired. In this study, we explore the DUP threshold that best discriminates subgroups with poorer outcome regarding global functioning and quality of life after 3 years of treatment.

Method: A total of 432 patients were followed-up prospectively over 3 years. Several hypothetical cut-off points for DUP were tested in order to maximize differences in effect size for quality of life and general functioning.

Results: While a DUP cut-off of 86 weeks defined two subpopulations with a difference of greatest effect size in quality of life after 3 years, it is already at a cut-off of 3 weeks of DUP that two subpopulations with a difference in global functioning of the greatest effect size was reached.

Conclusion: DUP seems to have a differential impact on the various components of outcome, and in particular on quality of life and global functioning. Our data suggest that aiming at very short DUP is justified, but that DUP over 3 weeks are still compatible with good quality of life after 3 years of treatment.

KEYWORDS

duration of untreated psychosis, early intervention, functioning, quality of life

1 | INTRODUCTION

Delay between psychosis onset and exposure to appropriate treatment or ‘duration of untreated psychosis’ (DUP), has been identified as a key target in specialized early intervention programs in the early phase of psychotic disorders (Joa et al., 2007; Melle et al., 2008; NHS, 2015). This is based on the assumption that its reduction may have a positive impact on the course of symptoms and functioning (Melle et al., 2008).

Several papers have shown DUP to be significantly associated with outcomes: these studies reported lower severity of symptoms, better functioning and quality of life, as well as higher remission rates in patients with shorter DUP (Kane et al., 2016; Malla et al., 2014; Marshall et al., 2005; Souaiby et al., 2016). In a sample of first-episode psychosis patients where the median DUP was 74 weeks, Kane et al. (2016) found that patients with DUP shorter than 74 weeks displayed a greater improvement in quality of life and psychopathology than those with longer DUP.

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Our previous research also suggested that DUP was significantly correlated with most aspects of functional outcomes at 12, 24, and 36 months, but not at 2 and 6 months (Golay et al., 2016). In addition, it was a significant predictor of symptomatic remission and functional recovery at discharge.

Available data suggests however that the association between DUP and outcomes is relatively modest and remains a matter of controversy (Craig et al., 2000; Harrigan et al., 2003; Ho & Andreasen, 2001). Harrigan et al. (2003) for instance did not find any link between DUP and course of illness, level of functioning, or symptoms severity 24 months after a first admission for psychosis. Nevertheless, it has been suggested that the limited predictive value of DUP in studies may be linked to definition issues (Polari et al., 2011) and whether DUP really comes to an end when patients enter a clinical program because many patients fail to engage and to take prescribed medication (Golay et al., 2016). In any case, shortening DUP under 12-week was recommended by the World Health Organization and the International Early Psychosis Association. It was also empirically validated by Dama et al. (2019) who showed that a short DUP within this interval was critical for symptom remission in early intervention settings. Cost-effectiveness was also much greater for patients with a DUP shorter than 12 weeks (Groff et al., 2021). However, while a short DUP seems intuitively and empirically desirable, little is known about the precise DUP threshold above which functional recovery becomes unlikely. There is also a lack of knowledge regarding potential differential impact on different dimensions of outcomes such as symptom remission, quality of life or functioning level.

The objective of this study was to determine the DUP threshold that best discriminates subgroups with poorer outcome regarding global functioning and quality of life after 3 years of treatment. The decision to focus on functioning and quality of life rather than symptomatology is based on the observation that these two dimensions are considered by patients to be more important to achieve than symptom remission (Bonsack, 2019; Oberholzer, 2021; Solhduj & Hermant, 2015).

2 | METHODS

2.1 | Participants

The Treatment and early Intervention in Psychosis Programme (TIPP) is a specialized Early Intervention (EI) program run by the Psychiatry Department of Lausanne University Hospital's, in Switzerland (Baumann et al., 2013).

Patients aged between 18 and 35, living in the hospital's catchment area (population about 350 000) and meeting the criteria for 'psychosis threshold' subscale in the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005) are eligible to be included in this program. Exclusion criteria are drug-induced or organic psychosis, clinically assessed intellectual disability and antipsychotic medication for more than 6 months prior to their referral to the program. A multidisciplinary team (including psychiatrists and case

management nurses) conduct an initial assessment to ensure the accuracy of inclusion criteria before admitting patients. This study is based on the data stemming from the prospective follow-up of 432 patients who had completed the 3 years treatment period by the end of 2020 and for which clinical data was available.

The principles of both case management interventions and assertive community treatment undertaken in outpatient settings are at the basis of the TIPP treatment. Over 3 years, case managers are available to patients up to twice a week. Patients are seen at least 100 times over the 3-year program, primarily by their case manager but also by a resident physician or an intern in psychiatry. Case managers and an experienced psychologist performed detailed evaluations of patients' past medical history, demographic characteristics, exposure to adverse life events, and their current symptoms and functioning using interviews and a structured questionnaire. All patients treated within the TIPP are fully assessed at baseline, after 2 months, 6 months and then prospectively every 6 months.

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Canton of Vaud (CER-VD; protocol #2020-00272). The data of all patients were used in the study if the latter did not explicitly object to the use of their data for research purposes. Only four patients refused the use of their clinical data for research.

2.2 | Measures

In order to be in line with most research in the domain, we defined DUP as the time between the onset of psychosis defined by the Comprehensive Assessment of At-Risk Mental States (CAARMS) instrument (Yung et al., 2005) and the admission to the TIPP. The psychosis threshold and its time are determined prior admission based on an expert consensus between the TIPP psychiatrists and case managers using information from medical or hospitalization reports from treating psychiatrists if available, as well as from the detailed report of the clinician who addressed the patient to the program. If the psychosis threshold cannot be determined clearly based on these reports, further specialized clinical assessments are conducted based on the structured interview for psychosis-risk syndromes (SIPS; McGlashan et al., 2001). Following this process, the clinical director of the TIPP completes the CAARMS. The CAARMS defines this psychotic disorder threshold as frank psychotic symptoms such as delusions, hallucinations and thought disorder persisting for longer than 1 week and with a frequency of at least 3–6 times a week for longer than 1 h each time or daily for less than 1 h each time. This is a standard and widely used criteria for first episode psychosis threshold (Nelson et al., 2014; Polari et al., 2011). We subdivided Patients' socioeconomic statuses into low, intermediate and high (Chandola & Jenkinson, 2000). The Case-managers used the Global Assessment of Functioning (GAF) instrument to estimate functional levels during the 3-year follow-up. It assesses a combination of symptoms and functioning. The Case-managers also used the Social and Occupational Functioning Assessment (SOFAS) in order to provide a measure that only takes the social

and occupational functioning into account, regardless of the intensity of symptoms. In this study, we used the endpoint GAF and SOFAS (36 months). The Case-managers assessed quality of life at discharge with the World Health Organization Quality Of Life assessment scale (WHOQOL GROUP, 1995, 1998), which is a 26-item self-rated scale measuring satisfaction with life and self-esteem based on 5-point Likert scales ranging from 1 (low satisfaction) to 5 (high satisfaction). The WHOQOL assesses self-perceived quality of life considering environment, social relationships, psychological and physical health. This instrument showed high internal consistency and coherent pattern of correlations with other validated psychiatric measures in French language patients in our region (Golay et al., 2019; Golay, Martinez, et al., 2021; Golay, Moga, et al., 2021). If quality of life after 36 months was not available, we used the 30 months value instead.

2.3 | Statistical analysis

In order to determine the threshold for DUP regarding impact on quality of life and general functioning, patients were distributed into short and long DUP subgroups with varying allocation rules. We then compared groups for differences in quality of life and general functioning using Cohen's *d* effect sizes. Several cut-off points to define high/low DUP were used, including (1) the 74 weeks median DUP of Kane's study (2016) which examined quality of life as an outcome, (2) our program's median DUP (12.5 weeks), and (3) a value obtained from an exhaustive search designed to maximize between group effect sizes. This algorithm computed and plotted all Cohen's *d* for every DUP cut-off between 0 and 1000 days with a resolution of 10-day intervals. Higher values on the plot allowed quick identification of cut-off values between high and low DUP yielding the greater effect size on quality of life and general functioning, respectively.

3 | RESULTS

The sample characteristics of the 432 patients are shown in Table 1.

A DUP threshold of 86 weeks yielded the most significant difference in the quality of life (600 days; $d = 0.80$; Figure 1). In our sample, only 21.1% (91) of the patients had a DUP equal or greater than 86 weeks. Examination of the curve also revealed that very short cut-offs were not associated with large differences in quality of life.

When the DUP cut-off was set at 74 weeks, the difference between patients above and below this threshold regarding quality of life at the end of the program was smaller although still large ($d = 0.72$). A total of 332 (76.9%) patients had a DUP shorter than 74 weeks.

When the DUP cut-off was set 12.5 weeks (our median DUP value), difference between patients above and below this threshold regarding quality of life at the end of treatment was smaller ($d = 0.36$).

A DUP threshold of 3 weeks yielded the most significant difference in GAF at the end of the program (20 days; $d = 0.45$; Figure 2).

TABLE 1 Sample characteristics ($N = 432$)

Characteristics	
Age, mean (SD), year	24.56 (4.69)
Gender, % (N), male	66.7 (288)
Socio economic status, % (N)	
Low	23.6 (102)
Intermediate	41.0 (177)
High	35.4 (153)
DUP, Mdn (IQR), weeks	12.57 (64.54)
Global Assessment of Functioning (GAF) at baseline, mean (SD)	41.84 (16.82)
Global Assessment of Functioning (GAF) after 36 months, mean (SD)	59.05 (15.83)
Social and Occupational Functioning Assessment (SOFAS) at baseline, mean (SD)	43.02 (15.87)
Social and Occupational Functioning Assessment (SOFAS) after 36 months mean (SD)	60.45 (15.53)
Quality of life (WHOQOL) after 2 months, ^a mean (SD)	73.85 (11.72)
Quality of life (WHOQOL) after 30/36 months, mean (SD)	82.84 (13.92)
Diagnosis	
Schizophrenia	57.4 (248)
Schizophreniform/brief	13.9 (60)
Schizoaffectif disorder	8.1 (35)
Major depression with psychotic features	3.7 (16)
Bipolar disorder	6.5 (28)
Others	10.4 (45)

Abbreviation: DUP, duration of untreated psychosis.

^aQuality of life was not available at baseline.

In our sample, 80.3% (347) of the patients had a DUP greater than 3 weeks.

Difference in GAF between patients with a low or high DUP was small ($d = 0.18$) according to the 74 weeks cut-off. The difference according to the 12.5 weeks cut-off was larger ($d = 0.34$).

Examination of the SOFAS revealed a pattern of results very similar to the GAF. The maximum difference in SOFAS was found when the cut-off was set to a value greater than 3 weeks; (20 days; $d = 0.42$; Figure 3). Difference between patients with a low or high DUP was small ($d = 0.12$) according to the 74 weeks cut-off. The difference according to the 12.5 weeks cut-off was larger ($d = 0.27$).

Because Post Hoc analysis revealed that patients with a diagnosis of schizophrenia were under-represented within patients with very short DUP (<3 weeks; 38.8% vs. 62.0%), analysis were repeated on data of patients with schizophrenia diagnosis only. The cut-off value for quality of life remained identical (86 weeks) but the effect size was slightly lower ($d = 0.66$). For GAF respectively the SOFAS, the cut-off associated with the greatest difference was slightly longer (8.6 weeks for both measures) and the effect size was lower ($d = 0.24$ and $d = 0.10$).

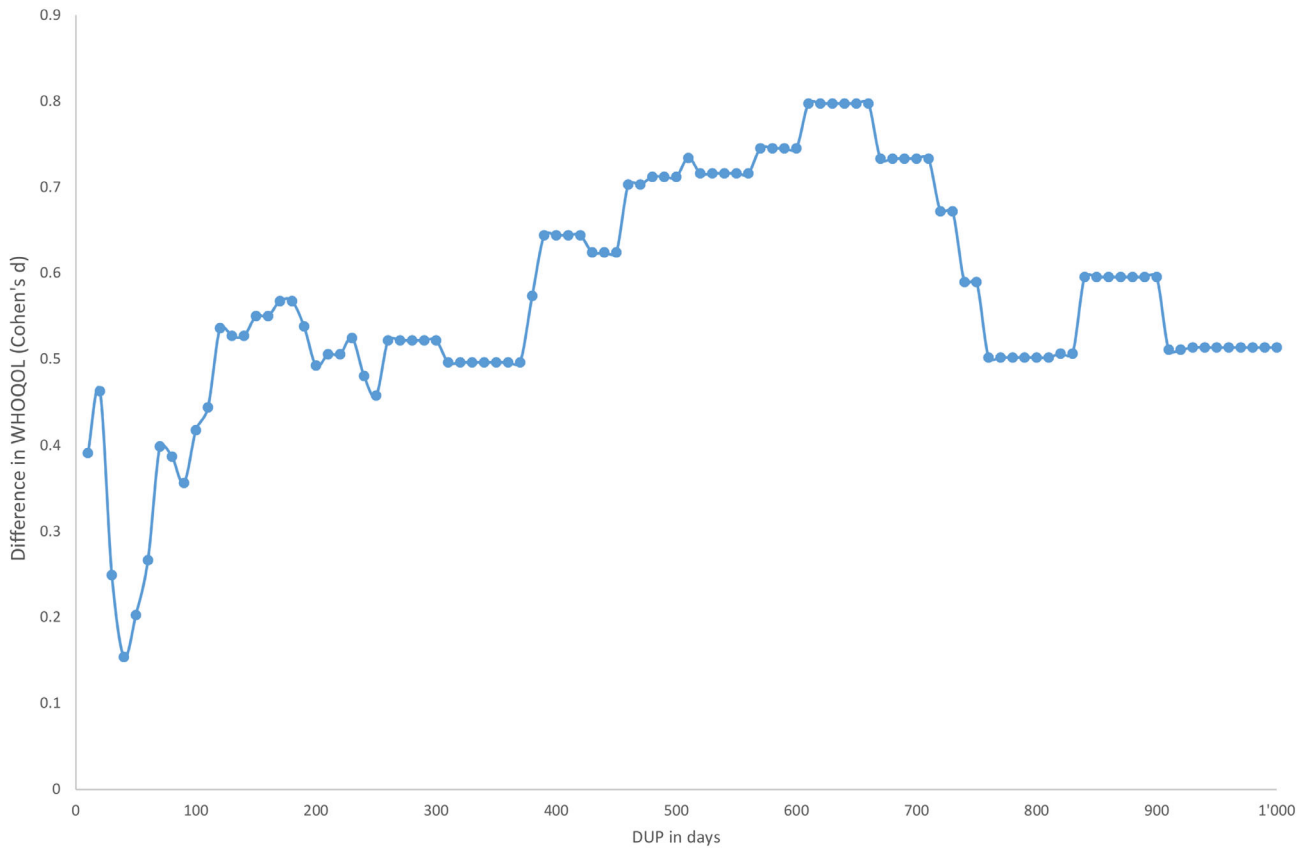


FIGURE 1 Difference in WHOQOL according to DUP

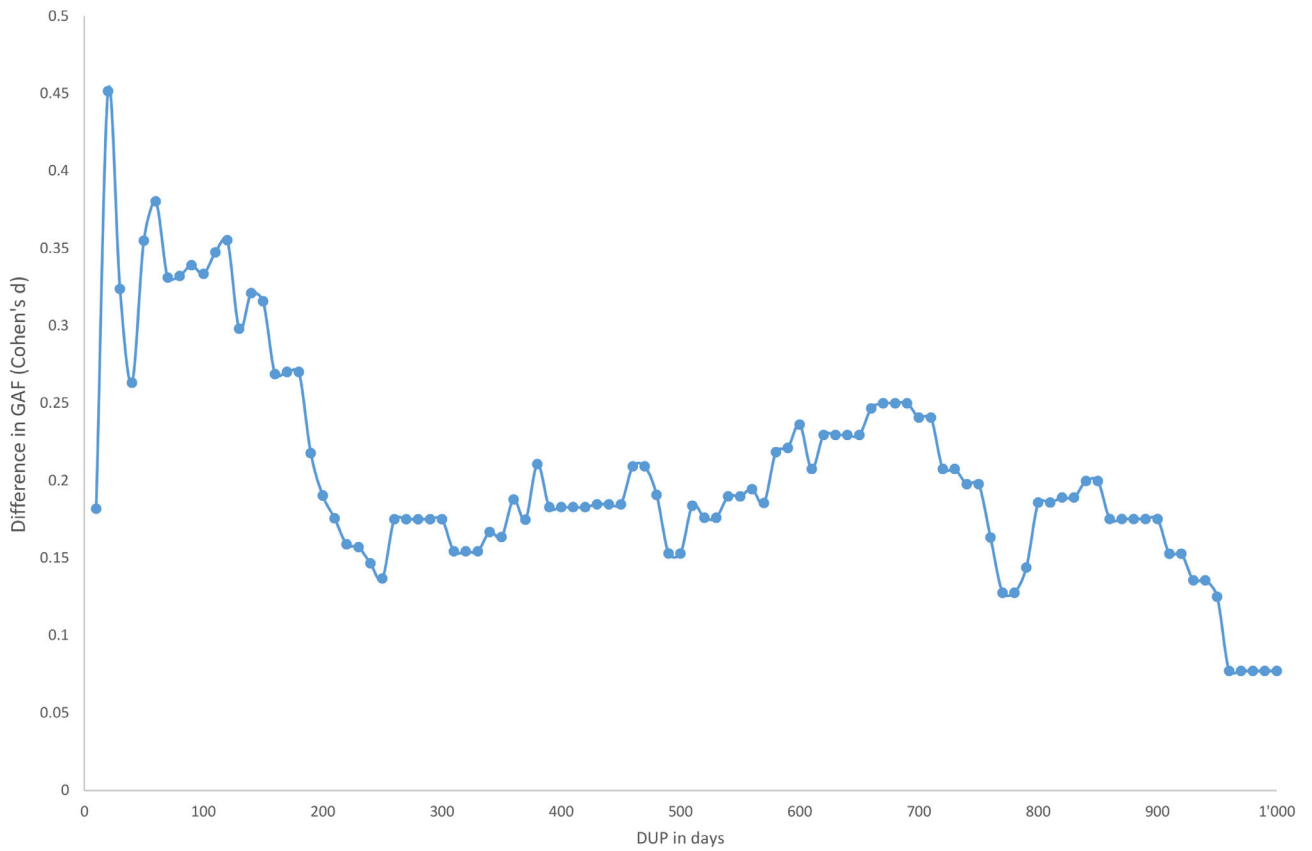


FIGURE 2 Difference in GAF according to DUP

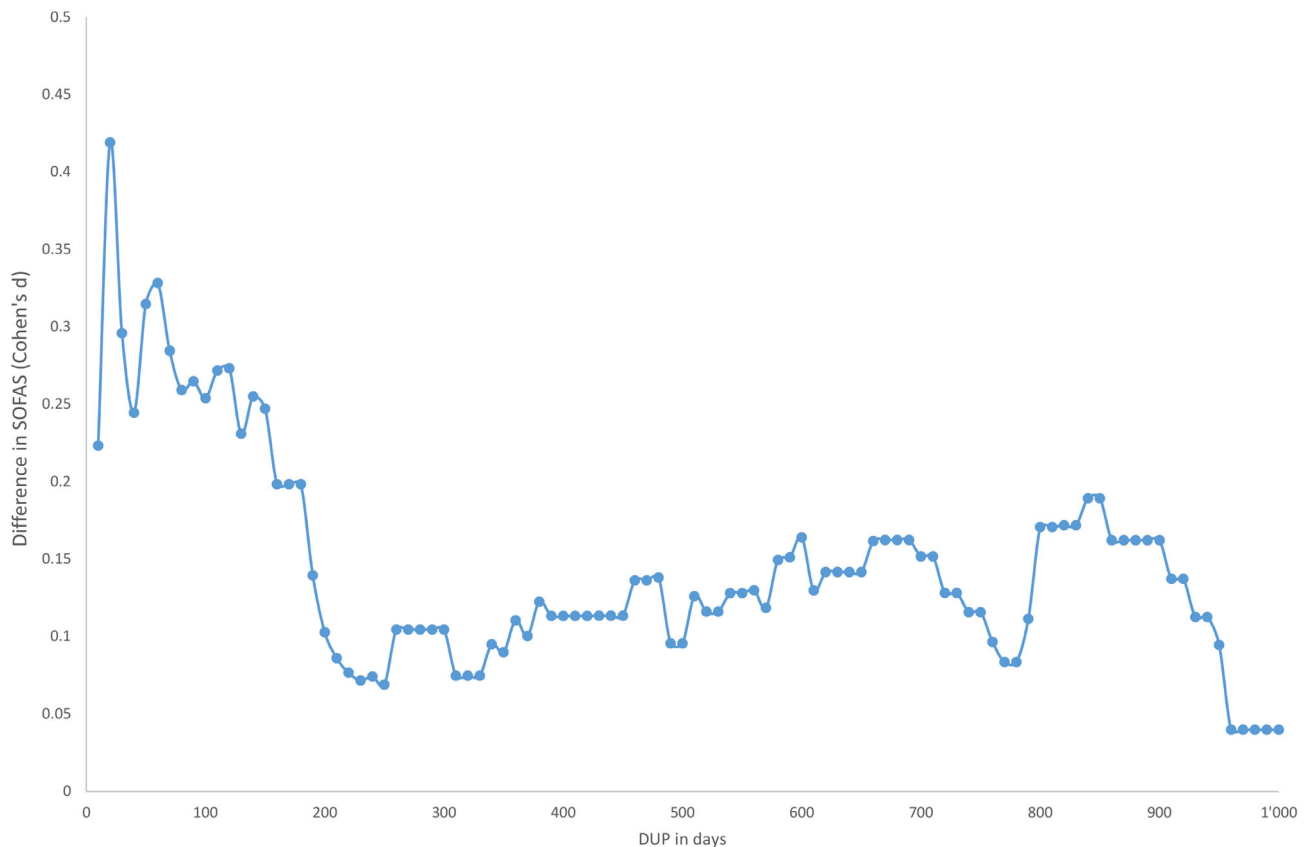


FIGURE 3 Difference in SOFAS according to DUP

4 | DISCUSSION

In the present study, we tried to identify the DUP value that best separated two populations of patients with the most significant outcome differences regarding quality of life and GAF and SOFAS scores. Because only very few patients refused the use of their clinical data for research, we consider the study sample to be highly representative of the population of patients with first-episode psychosis who need specialized psychiatric treatment. Our results show that the length of DUP has a different impact on WHOQOL and GAF/SOFAS scores. While the cut-off for DUP must be set at close to 1.5 years in order to separate two groups with clearly distinct outcomes regarding quality of life at the end of treatment, the threshold occurs already after only 3 weeks for the GAF and the SOFAS scores. Although attenuated, the same pattern of results is found when restricting analysis to patients with schizophrenia.

Taken together, these results suggest that the impact of DUP on outcome depends on the dimensions that are explored. Indeed, while GAF and the SOFAS are expert rated tools assessing a mix of function and symptoms on an objective way (American Psychiatric Association, 1994), WHOQOL is a self-assessment (WHOQOL GROUP, 1995, 1998) measuring subjective satisfaction of patients regarding various aspects of their life: these two domains seem to be very differently impacted by DUP. Based on this, we can draw two

main conclusions. First, when treatment aims are defined, according to the GAF or SOFAS, in terms of reduction of symptoms and return to activity, the impact of treatment delay is very high. If such are the treatment targets, programs should aim at DUP that do not exceed 3 weeks, which is in line with current recommendations for the treatment of first episode psychosis such as NICE for example (NHS, 2015). Second, when it comes to self-assessed quality of life, DUP seems to have a more limited impact. Indeed, while a shorter DUP seems preferable in this domain as well, the outcome difference for a cut-off of up to more than a year remains modest. This observation that only patients with very long DUP have a significantly poorer quality of life than the others at the end of the treatment period needs to be explored in more details. In addition to DUP, premorbid adjustment also seems to be associated to poorer quality of life (MacBeth & Gumley, 2008). We hypothesize that long DUP is linked to factors such as long-lasting social isolation and exposure to various forms of trauma for example, which in turn lead to global and profound deterioration of patients' situation and to conditions where integrated treatment remains ineffective to improve quality of life.

Taken together, these observations suggest that aiming at very short DUP is relevant in order to foster symptoms remission and return to activity (Golay et al., 2016; NHS, 2015). However, assuming that achieving a maximum DUP of 3 weeks could be a major challenge

for many programs that do not have sufficient resources, knowing that a good quality of life can be achieved despite longer DUP could nevertheless justify the implementation of integrated early intervention programs. Further studies are also needed in order to examine the pathway of impact of DUP on quality of life, especially regarding clinical outcome, which could mediate or moderate such a relationship. DUP may have both direct and indirect impact on functional as well as quality of life outcome.

Our study has several limitations that future studies should address. First, our exhaustive threshold search may be subject to random variation in the data and differences in subgroup sizes so that neighbouring cut-off may be an equally adequate value even if small effect size differences are apparent. Second, our analysis was limited to quality of life and general functioning that we considered as two very important outcomes. In further work, this should naturally be extended to other important outcomes such as symptomatology or risk of relapse that are also associated with DUP. However, general functioning as measured in the present study also captures the impact of symptomatology and provides a broad picture of social and professional functioning which has the secondary advantage of being easier to administer by clinicians (Golay, Romain, et al., 2021). Third, our measure of quality of life differed from the Kane et al. study (2016) which relied upon the Heinrichs' Quality of Life Scale, a 21-item scale based on a semi-structured interview designed to assess deficit symptoms (1984). Therefore, our quality of life measure could be considered as more subjective. It is likely affected by many non-clinical variables, some of these may be entirely external to the person or their illness. It is also worth noting that quality of life at baseline was not taken into account and is also likely substantially linked to long term outcome. Changes in these scores should also be a target for measuring the effect of DUP. Finally, our DUP measure was based on an expert consensus for the psychosis threshold between the clinicians of the specialized early intervention in psychosis program rather than on tools specifically designed to measure DUP. The measurement of DUP could also be dependent of memory of past events and be less reliable when the onset of psychosis is distant in time. Despite reliability of the DUP measure cannot be estimated, these clinicians are experts in the field and have received standardized training allowing us to believe that this measure is robust.

5 | CONCLUSIONS

DUP seems to have a differential impact on the various aspects of outcome after a first episode of psychosis, such as for example on quality of life and global functional level. Our results suggest in particular that very long DUP has an impact on quality of life while its effect on general functioning 3 years later is already important when it exceeds 3 weeks. While efforts must be pursued to shorten very long DUP in order to guaranty an acceptable quality of life, aiming at the maximum of 3 weeks proposed in current guidelines seems justified in order to allow return to good functional levels.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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