



Is processing speed a valid neurocognitive endophenotype in bipolar disorder? Evidence from a longitudinal, family study

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ARTICLE INFO

Keywords:

Bipolar disorder
Cognition
Endophenotype
Processing speed
Longitudinal study
Family study

ABSTRACT

Background: Substantial evidence supports the existence of neurocognitive endophenotypes in bipolar disorder (BD), but very few longitudinal studies have included unaffected relatives. In a 5-year, follow-up, family study, we have recently suggested that deficits in manual motor speed and visual memory could be endophenotype candidates for BD. We aimed to explore whether this also applies to processing speed.

Methods: A sample of 348 individuals, including 163 BD patients, 65 unaffected first-degree relatives (BD-Rel) and 120 genetically unrelated healthy controls (HC), was assessed with the Digit Symbol Substitution Test (DSST) on two occasions over a 2-year period (T1, T2). DSST values were controlled for age, years of education, occupational status, and subsyndromic mood symptoms. Differences between groups were evaluated with ANCOVAs.

Results: At T1 BD performed significantly worse than HC ($p < 0.001$; Cohen's $d = 1.38$) and BD-Rel ($p < 0.001$; Cohen's $d = 0.82$). BD-Rel showed an intermediate performance with significant differences with HC ($p < 0.01$; Cohen's $d = 0.50$). Similarly, at T2 BD performed significantly worse than HC ($p < 0.001$; Cohen's $d = 1.44$) and BD-Rel ($p < 0.01$; Cohen's $d = 0.51$). BD-Rel performance was intermediate and significantly lower than that of HC ($p < 0.01$; Cohen's $d = 0.97$). A Repeated Measures ANOVA revealed no significant between-group differences in performance over time ($p > 0.05$).

Conclusions: The results of this longitudinal, family study suggest that impaired processing speed may represent a suitable cognitive endophenotype for BD. Further research on the field is required to confirm these preliminary findings.

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<https://doi.org/10.1016/j.jpsychires.2021.07.008>

Received 18 February 2021; Received in revised form 30 June 2021; Accepted 5 July 2021

Available online 6 July 2021

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1. Introduction

Over the last decade, cognitive dysfunction in bipolar disorder (BD) has been extensively studied, and it is currently recognized as a core feature of the disorder (Martinez-Aran and Vieta, 2015). Moreover, cognitive impairment is consistently associated with poorer functional outcomes and impaired quality of life (Baune and Malhi, 2015; Depp et al., 2012; Jensen et al., 2016; Tabarés-Seisdedos et al., 2008; Tse et al., 2014).

Neuropsychological impairment has been observed in social and general cognition even in young individuals at genetic high risk for BD, specifically in the domains of visual memory, verbal memory, sustained attention and processing speed (PS) (Bora and Özerdem, 2017a). Several meta-analyses have also confirmed an impaired neurocognitive profile in unaffected relatives of BD patients (Bora et al., 2009; Bortolato et al., 2015). This has resulted in a growing interest to identify neurocognitive endophenotypes as trait-related illness biomarkers. Conventional criteria for cognitive measures to qualify as endophenotypes include the association of the disease within a population, heritability, state-independency, co-segregation and higher frequency in non-affected family members than in the general population (Gottesman and Gould, 2003; Leboyer et al., 1998). So far, the most consistent neurocognitive endophenotypes in BD encompass the domains of attention/concentration, verbal memory, and executive functions such as cognitive flexibility, verbal fluency, and working memory (Arts et al., 2008; Balanzá-Martínez et al., 2008; Bora et al., 2009; Bourne et al., 2013; Glahn et al., 2010; Vierck et al., 2015).

Regarding attention/concentration, processing speed (PS) deserves particular mention. PS is defined as the ability to identify, discriminate, integrate and respond to simple and complex information, and is considered to play a key role as a primary function subserving higher-order cognitive abilities (Frantom et al., 2008; Kieseppä et al., 2005; Salthouse, 1996; Weiss et al., 2016). Neuropsychological tests such as the Stroop Test, but mostly the Trail Making Test A (TMT-A), and the Digit Symbol Substitution Test (DSST) from the Wechsler Adult Intelligence Scale (WAIS) have been used to assess PS in neuropsychological studies of BD (Bora and Özerdem, 2017a,b; Miskowiak et al., 2017).

Several cross-sectional and follow-up neurocognitive and neuroimaging studies have described deficits on PS in BD patients (Lange-necker et al., 2010; López-Jaramillo et al., 2010; Nguyen et al., 2017; O'Donoghue et al., 2017; Samamé et al., 2014; Thompson et al., 2005; Torres et al., 2007). This data is confirmed by several meta-analyses in euthymic BD patients, including first episode of BD, with medium to large effect sizes for PS (Bora and Özerdem, 2017a; Lee et al., 2014; Robinson et al., 2006; Torres et al., 2007).

Regarding unaffected relatives of BD patients (BD-Rel), the importance of PS impairment measured through DSST is supported by several population-based sample studies. In two family studies with at least two members diagnosed with BD, impaired executive functioning and PS were shared by probands and their unaffected relatives (Antila et al., 2007, 2009). A study from the same group confirmed these findings, suggesting PS as a putative endophenotype of BD (Antila et al., 2011). In the same way, another family study found impaired DSST performance in both BD patients and BD-Rel (Daban et al., 2012). Finally, two large sample studies reinforce positive findings in familial studies. The first one assessed extended pedigrees and proposed working memory, facial memory and PS as putative endophenotypes with confirmed heritability (Glahn et al., 2010). The second sample, composed by two closely related, genetically isolated populations with at least one family member diagnosed with BD, confirmed significant additive heritability in verbal learning and memory, category fluency, inhibitory control and PS (Fears et al., 2014).

Conversely, other family studies found that PS as measured with the DSST is spared in BD-Rel. In a family study of unaffected siblings of youth with BD, neurocognitive impairments in executive functions, but not in PS or verbal learning were suggested (Doyle et al., 2009).

Similarly, a comparative study between Schizophrenia and BD, excluded PS as a potential endophenotype of BD, proposing in turn verbal memory, visual memory and auditory attention (Kremen et al., 1998). In the same way, PS was excluded as candidate in a short report of neurocognition in BD-Rel, announcing instead declarative memory and executive control as putative endophenotype candidates (Ferrier et al., 2004). Finally, a comparative study of BD-only or BD-mixed families found no differences between HC and any BD-Rel group (McIntosh et al., 2005).

Of note, family studies showed heterogeneity in terms of sample size, sample composition of patients and relatives' groups, neurocognitive batteries and statistical analysis, although the study design was cross-sectional in all cases. In sum, the endophenotypic nature of PS in BD remains uncertain based on available cross-sectional, family studies (Cardenas et al., 2016; Miskowiak et al., 2017).

Demonstrating the stability of neurocognitive impairments in unaffected relatives may further strengthen its link with genetic risk for BD. In this regard, family studies with a longitudinal design have been proposed as a helpful strategy to identify consistent neurocognitive endophenotypes in severe mental illness (Luperdi et al., 2019). However, so far only two studies have used this approach in BD to assess manual motor speed and visual memory functions (Correa-Ghisays et al., 2017, 2019). This certainly represents a research gap in the field.

Therefore, the present study aims to examine whether PS represents a putative endophenotype for BD based on a longitudinal, family design. We hypothesized that BD probands and their unaffected relatives would show a persistent deficit on PS over a short-term trajectory whereas the performance of their unaffected family members would fall between that of patients and healthy controls.

2. Materials and methods

This study is part of an ongoing neurocognitive investigation of severe mental disorders, carried out by CIBERSAM/TMAP-UV G24 in Valencia, Spain. In this follow-up study, sociodemographic, clinical, cognitive and functional data were obtained simultaneously (Balanzá-Martínez et al., 2008; Correa-Ghisays et al., 2017; Salazar-Fraile et al., 2009; Selva-Vera et al., 2010; Tabarés-Seisdedos et al., 2008). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The Ethics Committee of the University Clinical Hospital of Valencia reviewed and approved the study design, and all participants provided written informed consent after the nature of the procedures had been fully explained.

In order to assess the short-term neurocognitive trajectory, assessments were repeated 1–2 years (T2) after baseline (T1).

2.1. Participants

The patients and their relatives (parents, siblings, offspring) were recruited from a hospital in the city of Valencia and six community mental health centers in the province of Valencia, Spain. Healthy controls were recruited by word of mouth in the same areas of residence of patients.

All participants were aged 18–65 years. Left-handed individuals were excluded from the analysis, as they were a small minority and to reduce potentially biased performance (Nicholls et al., 2010).

The diagnosis of BD was made by expert psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders – DSM IV –TR (American Psychiatric Association, 2000). All BD were in remitted patients at the time of evaluation and had not received ECT within the last 12 months. BD-Rel had to fulfill the following criteria: 1. No personal history or current diagnosis of severe mental disorder; and 2. Currently not taking psychotropic medication. In addition, healthy controls (HC) had to present no family and personal history of psychotic or mood disorders.

The exclusion criteria for all participants in this study were: 1.

Presence of any neurological disorder, history of brain injury or any medical condition that could interfere with test cognitive performance; 2. Intellectual disability (IQ < 70), as estimated with the Vocabulary subtest from the Wechsler Adult Intelligence Scale (WAIS III); 3. Current substance use disorder, except for nicotine, or being under the influence of any substance at the time of assessment.

2.2. Sociodemographic and clinical assessment

At both assessments, sociodemographic data included sex, age, occupational status, and years of education. For patients, clinical data were age of illness onset, family history of mental illness, type of psychopharmacological treatments. Mood state was rated by means of the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960; Ramos-Brieva and Cordero-Villafafila, 1988), and the Young Mania Rating Scale (YMRS) (Young et al., 1978; Colom et al., 2002). Euthymia was psychometrically confirmed with total YMRS total score <6 and HRSD total score ≤8.

2.3. Neuropsychological assessment

Participants were assessed with the Digit Symbol Substitution Test (DSST) from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1997). DSST is a paper-and-pencil test that requires a subject to match symbols to numbers according to a key located on the top of the page, and to the symbol into spaces below a row of numbers. The final score is based on the number of correct symbols copied within the allowed time, which was 120 seconds in this study. As a result of its brevity, sensibility, reliability, minimal impact of language, culture, and education on test performance, DSST is among the most extensively used and validated cognitive tests in neuropsychology. It has been widely employed to assess PS and other cognitive functions related with PS, such as working memory, attention and visuospatial functions (Gallagher et al., 2014; Jaeger, 2018).

2.4. Statistical analysis

An Exploratory Data Analysis (EDA) was performed for all variables in order to evaluate its normality and accuracy. A regular ANCOVA test was performed for DSST values at T1 with age, years of education, occupational status, and subsyndromic mood symptoms (YMRS and HRSD) as covariates. These variables were chosen as they presented significant differences between groups. Effect sizes were assessed with Cohen's d value.

For assessing the variability of the test values in each group, multiple comparisons between groups and times were assessed using the Tukey's post-hoc test with Bonferroni correction. In the case of potential confounders, the Tukey range test was used in conjunction with the ANCOVA test for the first assessment of each participant.

A Repeated measures ANOVA was performed to assess the evolution of DSST over time among groups.

All statistical analyses were performed in R language (version 3.3.1) (R Core Team, 2016).

3. Results

A total of 348 participants were assessed at T1 (163 BD, 65 BD-Rel and 120 HC), of whom 218 were examined at T2 (113 BD, 11 BD-Rel and 94 HC). At T1, the BD-Rel sample was composed by 8 parents, 46 siblings, and 11 offspring.

Sociodemographic and clinical characteristics of the sample at T1 are shown in Table 1. There were no significant sex differences among the groups. Conversely, age, years of education and occupational status showed significant differences among groups. Regarding clinical variables, YMRS and HRSD scores significantly differed between groups. Treatment variables, psychiatric family history and age at onset of

Table 1
Sociodemographic and clinical characteristics of groups.

Variables	BD (N = 163)	BD-Rel (N = 65)	HC (N = 120)	F	P
Sex (male)	64 (39.26)	22 (33.85)	46 (38.33)	0.59 ^a	0.74
Age (years)	43.68 ± 10.68	43.36 ± 12.37	36.41 ± 12.67	14.73	<0.001
Years of Education	10.93 ± 4.28	11.85 ± 4.37	14.28 ± 3.72	23.11	<0.001
Occupational status (active)	41 (25.15)	46 (70.76)	104 (86.67)	107.43 ^a	<0.001
YMRS	2.51 ± 3.51	0.59 ± 1.48	0.40 ± 0.96	22.95	<0.001
HRSD	4.45 ± 4.18	2.27 ± 3.97	1.99 ± 2.58	15.71	<0.001
Age at onset of Disease (years)	27.88 ± 9.28				
Psychiatric Family History	106 (65.03)				
Antipsychotics	71 (43.56)				
Antidepressants	41 (25.15)				
Lithium	79 (48.47)				
Carbamazepine	19 (11.66)				
Benzodiazepines	76 (46.63)				

Note: Data are presented as n (%), except for quantitative variables: mean ± SD. Abbreviations: BD, Bipolar disorder patients; BD-Rel, Bipolar disorder Relatives; HC, Healthy Controls; YMRS, Young Mania Rating Scale; HRSD, Hamilton Rating Scale for Depression.

^a Pearson's chi-squared test.

disease were not associated with significant differences in DSST performance ($p > 0.05$). Despite sample attrition at T2, no significant differences were found in sociodemographic variables between T1 and T2.

3.1. Neurocognitive performance

At T1, ANCOVA revealed significant differences between the three groups in DSST performance (Table 2). BD patients performed significantly worse than both BD-Rel ($p < 0.001$; Cohen's $d = 0.82$) and HC ($p < 0.001$; Cohen's $d = 1.38$). The BD-Rel group performance was intermediate between BD and HC, with significant differences in DSST performance between BD-Rel and HC ($p < 0.01$; Cohen's $d = 0.50$).

Table 2
Between-group comparison of performance on the DSST at both assessments.

Group	BD	BD-Rel	HC	F	P	Post-hoc
T1 ^a	9.81 ± 3.24	12.60 ± 3.67	14.30 ± 3.31	7.84	<0.001	BD < HC ** BD < BD-Rel ** BD-Rel < HC *
T2 ^b	9.96 ± 3.84	11.90 ± 3.27	15.20 ± 3.39	11.29	<0.001	BD < HC ** BD < BD-Rel * BD-Rel < HC *

ANCOVA analysis for differences among groups, adjusted for age, education, occupational status, YMRS and HRSD. BD: Bipolar disorder patients; BD-Rel: Bipolar disorder relatives; HC: Healthy controls. Data are presented as mean ± SD.

* $p < 0.01$. ** $p < 0.001$.

^a BD (n = 163), BD-Rel (n = 65), HC (n = 120).

^b BD (n = 113), BD-Rel (n = 11), HC (n = 94).

At T2, sample attrition was mostly observed in the BD-Rel group. Again, significant differences were found between the three groups (Table 2). Performance in DSST was significantly lower in BD compared to both BD-Rel ($p < 0.01$; Cohen's $d = 0.51$) and HC ($p < 0.001$; Cohen's $d = 1.44$). BD-Rel performance was intermediate between BD and HC, with significant differences between BD-Rel and HC ($p < 0.01$; Cohen's $d = 0.97$).

3.2. Between-comparison of DSST performance over time

The between-comparison of DSST performance over time was assessed under a Repeated Measures analysis (Fig. 1) in those participants with complete evaluations in T1 and T2. The within-group trajectories revealed no significant differences in BD patients and BD-Rel ($p > 0.05$). Conversely, HC trajectories significantly differed over time ($p < 0.05$). A Repeated Measures ANOVA revealed no significant between-group differences in performance over time ($p > 0.05$).

4. Discussion

To our knowledge, this is the first longitudinal, family study including patients, BD-Rel, and healthy controls to evaluate whether PS represents a valid endophenotype candidate in BD.

The main finding was that both BD patients and their unaffected relatives had a significantly lower PS performance than HC at both assessments, which supports the short-term persistence of impaired psychomotor speed in both groups. Therefore, the present results suggest that impaired PS is a putative endophenotype and a putative marker of genetic vulnerability in BD.

PS fulfilled Gottesman and Gould's criterion of *association within a population*. After controlling for sociodemographic and clinical variables at T1 and T2, BD patients and their unaffected relatives showed a deficit in DSST. Consistent with these findings, several meta-analyses of cross-sectional and longitudinal studies have described slower PS in BD patients (Robinson et al., 2006; Samamé et al., 2014; Torres et al., 2007), first BD episodes (Lee et al., 2014), and also in BD-Rel (Cardenas et al., 2016; Bora, 2017). Notwithstanding, the association of psychomotor slowing with other cognitive deficits must be taken into account, including deficits in executive functioning (Lee et al., 2014; Mora et al., 2013; Robinson et al., 2006; Torres et al., 2007), attention (Chaves et al., 2011; Lee et al., 2014; Robinson et al., 2006), episodic memory (Torres

et al., 2007), and verbal learning (Robinson et al., 2006). These associations may highlight PS polyfactorial nature and characterization as a measure of generalized cognitive deficit (Dickinson et al., 2007), and may possibly hinder the identification of other types of cognitive impairments underlying PS. Nonetheless, the assessment of other cognitive functions beyond PS was not the aim of this study.

Our study's longitudinal approach and the short-term stability of PS impairment in patients, support the *state-independency* criterion. PS slowing has been associated with lower quality of life and functioning in BD patients (Mur et al., 2008; Sanchez-Moreno et al., 2018; Tatay-Manteiga et al., 2019). The persistent deficit in PS in BD patients is consistent with several reviews and meta-analyses (Bora, 2017; Bora and Özerdem, 2017; Samamé et al., 2014; Van Rheenen et al., 2020) and with previous neurocognitive longitudinal studies in patients (Chaves et al., 2011; Demmo et al., 2017; Mur et al., 2008; Santos et al., 2014).

A recent 3-year, follow-up study of patients with a first manic episode and matched controls, analyzed cognitive trajectories in several functions. Specifically, PS performance improved over the first year with a subsequent stabilization in the long-term (Torres et al., 2020). Unfortunately, our study could not confirm accurate longitudinal trajectories of PS performance in patients or relatives.

The milder deficit of PS in relatives suggests its correspondence with the *co-segregation* criterion and with the higher frequency of the deficit in unaffected family members than in the general population. As hypothesized, our findings converge with previous studies with either larger sample sizes (Daban et al., 2012; Fears et al., 2014; Glahn et al., 2010) or multiplex families, e.g., those with more than two affected members (Antila et al., 2007, 2009; Fears et al., 2014; Glahn et al., 2010), which suggests the influence of genetic load on PS (Kosger et al., 2015). Collectively, these findings support impaired PS as a putative endophenotype of BD, in accordance with a recent systematic review (Cardenas et al., 2016).

On the other hand, our findings diverge from other studies of BD-Rel (Arslan et al., 2014; Doyle et al., 2009; Ferrier et al., 2004; Kremen et al., 1998; McIntosh et al., 2005; Nehra et al., 2014; Pattanayak et al., 2012) and systematic reviews supporting that impaired PS would not represent a suitable candidate in BD (Miskowiak et al., 2017). Such controversy might be explained by several methodological differences across studies regarding neurocognitive batteries, statistical analysis, and sample size and composition. In particular, the high sensitivity and low specificity of the DSST (Jaeger, 2018) may contribute to inconsistent findings in

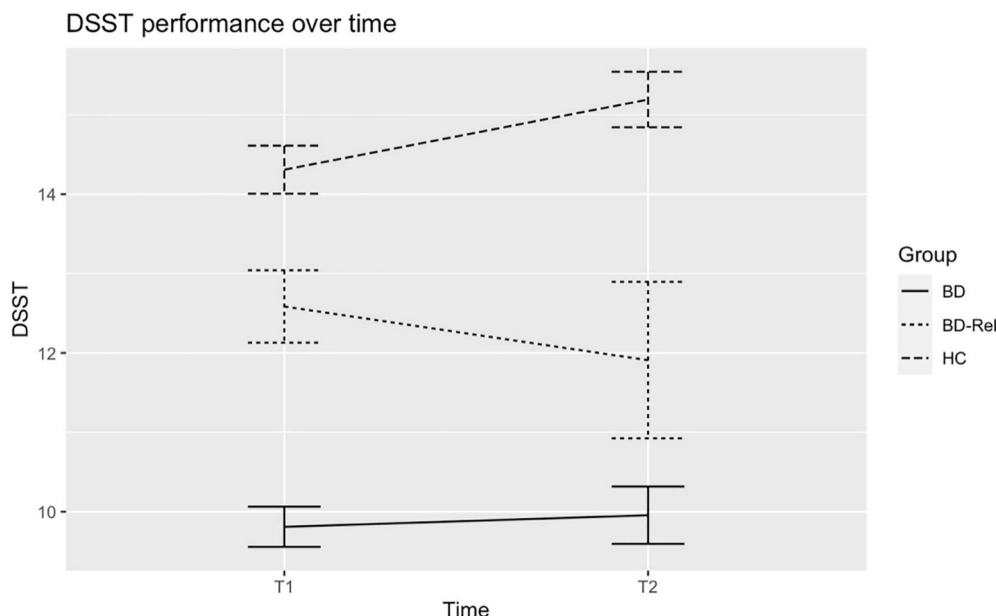


Fig. 1. Evolution of DSST for groups over time.

unaffected relatives of BD (Cardenas et al., 2016; Miskowiak et al., 2017).

The scientific strength provided by the longitudinal design of this study and the detailed analysis of the findings lead us to suggest impaired PS as a putative endophenotype in BD, with clinical implications as a potential marker of genetic vulnerability for BD.

It is suggested that longitudinal, family studies may represent a complementary, yet more demanding, approach to identify suitable neurocognitive endophenotypes for BD (Luperdi et al., 2019). In this regard, this study is among the few that have used this design in BD (Correa-Ghisays et al., 2017, 2019). The effect of several potential confounders on DSST performance was controlled for in the analysis, including subsyndromic mood symptoms. The presence of residual manic and depressive symptoms may further impair cognition in euthymic patients (Bourne et al., 2013) and unaffected relatives (Ferrier et al., 2004). The strict control of these symptoms across all three groups represents another study strength and emphasizes that approach in family, neurocognitive studies.

The results of the present study must be interpreted with caution due to several methodological limitations. First, substantial sample attrition, especially in the BD-Rel group, might explain at least in part the present results and may reduce the statistical power. Thus, our results may be seen as inconclusive rather than positive. In most cases, study participants were lost to follow-up or declined to participate. Second, our study employed the DSST as a single instrument of PS assessment, hindering the comparison of performances with other tests. Third, concerning the patient's group, moderators such as chronicity, stage of illness, number of episodes, and other clinical variables such as obesity and metabolic disorders were not considered (Mora et al., 2017; Solé et al., 2017). Fourth, our study did not take into consideration the remarkable cognitive heterogeneity which has been demonstrated in both patients with BD and their unaffected relatives (Russo et al., 2017; Van Rheenen et al., 2020). Fifth, comorbid psychiatric conditions such as ADHD may further compound the neurocognitive dysfunction associated with BD (Balanzá-Martínez et al., 2010) but were not controlled in this study. Moreover, the relatively reduced sample size prevented the establishment of cognitive clusters based on PS performance.

5. Conclusions

In conclusion, this family, follow-up study provides tentative evidence that impaired PS might be considered as an endophenotypic marker of genetic vulnerability for BD. However, substantial sample attrition may have biased the present results, hence the results must be considered inconclusive and preliminary, rather than positive. To ultimately reduce the impact of cognitive impairment in patients and families' global functioning, further longitudinal family studies with larger sample sizes and more extended follow-up periods are warranted (Allott and Van Rheenen, 2020; Szmulewicz et al., 2020).

Role of the funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

Dr Vicent Balanzá-Martínez has been a consultant, advisor or Continuing Medical Education (CME) speaker over the last 3 years for the following companies: Angelini; Ferrer; Lundbeck; Nutrición Médica; and Otsuka. None of the remaining authors declare any potential conflicts of interest.

CRedit authorship contribution statement

Sussy C. Luperdi: Conceptualization, Writing – original draft,

Visualization. Patricia Correa-Ghisays: Investigation, Writing – review & editing. Joan Vila-Francés: Formal analysis, Data curation. Gabriel Selva-Vera: Investigation, Writing – review & editing. José Salazar-Fraile: Investigation, Writing – review & editing. Narcís Cardoner: Writing – review & editing. Miguel Ruiz-Veguilla: Writing – review & editing. Lorenzo Livianos: Writing – review & editing. Rafael Tabarés-Seisdedos: Conceptualization, Writing – review & editing. Vicent Balanzá-Martínez: Conceptualization, Writing – original draft, Writing – review & editing, Supervision, All authors critically reviewed content and approved final version for publication.

Acknowledgements

Dr Vicent Balanzá-Martínez acknowledges the support from Instituto de Salud Carlos III (PI16/1770, PROBILIFE Study). The authors express their gratitude to all individuals who participated in this study and to the anonymous referees, whose comments helped to improve the quality of the paper.

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