Title:
Psoriasis and sleep:
an integrated clinical and cognitive approach

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1. Background and rationale

Psoriasis is among the most common dermatological pathologies, with a prevalence of about 2-4% in the general population (Gudjonsson et al., 2012). It is considered a systemic disease because of its complex pathogenesis and multiple comorbidities, among which sleep impairments appear to play a crucial albeit underestimated role. Indeed, sleep disruption is reported in up to 85% of psoriatic patients (Henry et al., 2019) and prevalence of inadequate sleep is remarkably higher among individuals with psoriasis compared to the general population (Wong et al., 2017; Jensen et al., 2018). In a large cohort study, self-reported sleep difficulty and low sleep quantity revealed a strong, graded association with psoriasis severity (Smith et al., 2019). Several factors have been proposed to contribute to sleep dysfunction in this population, including impaired thermoregulation (Nowowiejska et al., 2021), night-time itch (Wong et al., 2017), pre-sleep arousal (Henry et al., 2019) and low mood (Henry et al., 2016). Moreover, some authors underline that the links between sleep issues and psoriatic pathology are bidirectional, e.g., through inflammatory pathways (Myers et al., 2021) as well as psychological and psychosocial mechanisms (Nowowiejska et al., 2021). However, despite the wide literature produced on the topic, a clear characterization of sleep disruption in psoriasis is still lacking. As underlined in Henry et al.’s systematic review (2016), high quality empirical evidence is still very scarce. In fact, the great majority of studies lack hypothesis-driven research questions or have not employed validated measures of sleep. To this day, less than 10 studies have assessed sleep in psoriatic samples through objective measurements (i.e., polysomnography, actigraphy) and these have focused on obstructive sleep apnea rather than general sleep quality (e.g., Karaca et al., 2013), have exclusively relied on actigraphy rather than polysomnography (e.g., Henry et al., 2020), or have assessed psoriatic participants with no comparison to a control group (e.g., Papadavid et al., 2013). This dearth of research appears surprising considering the elevated health risks associated to chronic poor sleep. Indeed, chronic sleep dysfunction may entail a variety of adverse health outcomes, such as cardiovascular disease, obesity, type 2 diabetes, depression (Itani et al., 2017). This is particularly concerning in psoriatic populations since psoriasis is independently associated to many of the same comorbidities (Shah et al., 2017). Also, sleep impairments deeply affect daytime functioning, by reducing vigilance, concentration and cognitive performance (Killgore, 2010). Cognitive functioning in psoriasis has been seldom investigated. A few studies show that, compared to healthy controls, psoriatic patients display performance deficits in most cognitive domains: attention, visuo-spatial skills, declarative memory, executive functioning (Colgecen et al., 2016; Marek-Jozefowicz et al., 2017; Innamorati et al., 2018). However, no study has assessed the possibility that, in the psoriatic population, these cognitive impairments may be linked to poor sleep quality. Though understudied, impaired sleep and daytime functioning are plausibly crucial determinants of low quality of life in psoriatic populations (Nowowiejska et al., 2021). According to recent “syndemics approach” (Singer et al., 2017), psoriasis and sleep disturbance could be considered syndemics, rather than merely comorbid, since they are mutually influential on both physiological and psychosocial level. This conceptualization underlines their being linked in a vicious cycle and, simultaneously, the possibility that they can be exacerbated or alleviated at the same time. In this perspective, behavioral treatment of sleep disturbance appears as a viable path to explore with the aim to reduce both sleep impairment and general symptom burden in psoriasis. Indeed, Cognitive-Behavioral Therapy for Insomnia (CBT-I) has shown to be efficacious in improving sleep quality in patients with insomnia comorbid with several psychiatric and medical conditions (Wu et al., 2015 for a meta-analysis), with an effect extending to comorbid outcomes (Wu et al., 2015). Along this line, an interesting possibility could be to explore the effects of cognitive training, compared to standard CBT-I, on sleep quality in this population. In fact, in the last decades, sleep research has repeatedly highlighted that bedtime cognitive activity sessions are beneficial to subsequent sleep both in healthy and sleep-impaired samples (Cerasuolo et al., 2020). For instance, bedtime tasks appear to consistently enhance slow wave sleep parameters (e.g., Morita et al., 2012) and spindle activity (e.g., Fogel
& Smith, 2006), as well as to promote sleep continuity (e.g., Haimov & Shatil, 2013), stability (e.g., Arzilli et al., 2019) and cyclic organization (e.g., Cerasuolo et al., 2020).

2. Trial objectives and purpose

2.1. Primary Objective

The main objective of the present project is to address the impact of sleep impairments in psoriasis since sleep quality represents per se an important aspect of well-being which appears to be directly affected by the psoriatic pathology. On the other hand, sleep impairments probably represent a maintaining factor in psoriasis by hampering other facets of health (e.g., daytime cognition and stress levels) and ultimately resorting in worsening of symptomatology and of general quality of life.

2.2. Secondary Objective

To explore the hypothesized bidirectional relationship between psoriatic symptoms and sleep quality. This interplay will be investigated by:

a) performing the first comprehensive analysis of subjective and objective sleep quality in psoriatic patients: specifically, individuals with mild psoriasis will be selected, in order to explore the possible presence of subtle sleep impairments even in patients with low symptom severity, in whom the contribution of external sources of disturbance to sleep (e.g., itch, pain) is minimized. The analysis of classical sleep quantitative variables (such as sleep onset latency, sleep duration, sleep states proportion) will be complemented by a set of parameters which have been shown to more accurately describe sleep quality and to sustain sleep-dependent learning processes (i.e., sleep continuity, stability and cyclic organization variables (Conte et al., 2021); moreover, actigraphic monitoring performed over a week will allow to explore the stability of sleep-wake patterns of psoriatic patients over time; finally, comparisons of sleep features between psoriatic and non-psoriatic poor and good sleepers will allow to highlight possible peculiarities of the sleep profile linked to psoriatic disease;

b) conducting, in this population, a thorough assessment of cognitive functioning and investigating its possible relationships to sleep quality as well as possible differences in cognitive profiles between psoriatic and non-psoriatic poor and good sleepers;

c) assessing, in psoriatic individuals compared to healthy poor sleepers, the effect of 3 types of interventions focused on sleep improvement (i.e., classical Cognitive-Behavioral Therapy for Insomnia (CBT-I), bedtime cognitive training (BCT), and combined CBT-I + BCT) on subjective and objective sleep quality, daytime cognition, symptom severity and quality of life.

The significance of this research is manifest: a clearer understanding of the actual impact of sleep dysfunction in psoriatic patients and especially on their daytime functioning and quality of life will contribute to better orientate clinicians’ attention in devising the best treatments in this population. Furthermore, if a beneficial effect of CBT-I were obtained, this would encourage the inclusion of CBT-I protocols among the viable, evidence-based non-pharmacological treatments for dermatological care of this kind of disease. Finally, our investigation of the efficacy of cognitive training to improve sleep bears especially relevant applicative implications. In fact, the use of self-administered bedtime cognitive tasks as a behavioral treatment option in pathologies such as psoriasis could represent a very promising avenue to increase feasibility and compliance to non-pharmacological interventions when classical structured therapy protocols are difficult to implement.

3. Trial design

This is a low intervention level, non-pharmacological, multicentric, no-profit study that will entail two phases.
Phase I is aimed to obtain descriptive data about subjective and objective sleep quality (i.e., through actigraphic and polysomnographic - PSG –recordings) cognitive functioning and quality of life in 4 groups of participants:
A) healthy poor sleepers
B) psoriatic patients with complaints of poor sleep
C) psoriatic patients without complaints of poor sleep
D) healthy controls.

In Phase II, groups A and B (poor sleepers and psoriatic patients with sleep complaints, respectively) will undergo a randomized control trial (RCT), aimed to assess the effect of 3 types of cognitive functioning intervention (CBT-I, BCT, combined CBT-I + BCT versus a control condition) on subjective and objective sleep quality, cognitive functioning and quality of life. The effect of these interventions on symptom severity will also be assessed in the psoriatic patients. Specifically, the 4 sets of dependent variables (i.e., subjective and objective sleep quality, cognitive functioning, dermatological symptoms severity, quality of life) will be evaluated at T0 (before the intervention, i.e., during Phase 1 of the project), T1 (at the conclusion of the 8-weeks treatment), and T2 (at a 3-months follow-up).

3.1. Methodology
Study population
Psoriatic patients will be screened and recruited by an expert physician at the Dermatology Unit, University of Campania “Luigi Vanvitelli” and at the Dermatology section of the Department of Health Science, University of Florence.

Inclusion criteria for both psoriatic groups (B and C) will be:
- age range 18-50 years,
- a signed informed consent,
- a diagnosis of psoriasis made by an expert clinician, mild symptom severity (i.e., score at the Psoriasis Area and Severity Index (PASI, Fredriksson & Pettersson, 1978) < 10 and Dermatology Life Quality Index (DLQI; Finlay & Kahn, 1994) < 5),
- a wash out period of at least 2 weeks from topical treatment and 4 weeks from systemic treatment,
- absence of comorbid medical conditions (including psychiatric diagnoses, sleep disorder diagnoses, heart rate disorders and pathological motor activity),
- no history of drug or alcohol abuse,
- limited caffeine (no more than 150 mg/day) and alcohol (no more than 250 mL/day) consumption.

Participants will then be assigned to group B or C according to their score at the Pittsburgh Sleep Quality Index (PSQI, Italian version, Curcio et al., 2013), which yields a cut-off score of 5, with scores >5 indexing poor subjective sleep quality (Buysse et al., 1989).

As for control participants (groups A and D), they will be recruited from the general population through social media and ads on university websites and will be screened through a brief ad hoc interview (conducted by a psychologist) to collect general demographic data and information on medical conditions and health habits (including questions on somatic and psychiatric disorders, sleep habits and disturbances, substance use, as well as the administration of the PSQI).

Inclusion criteria of control participants (groups A and D) will be:
- age range 18-50 years,
- a signed informed consent,
- absence of clinical somatic or psychiatric conditions (including sleep disorders, heart rate disorders and pathological motor activity),
- no history of drug or alcohol abuse,
- limited caffeine (no more than 150 mg/day) and alcohol (no more than 250 mL/day) consumption.

Again, assignment to Group A or D will depend on scores at the PSQI.
Exclusion criteria for psoriatic patients will be:
- age < 18 and > 50,
- inability to give an informed consent,
- a diagnosis of moderate-severe psoriasis (PASI > 10 and DLQI >5),
- presence of systemic treatment and/or on topical treatment only,
- presence of comorbid medical conditions (including psychiatric diagnoses, sleep disorder diagnoses, heart rate disorders and pathological motor activity),
- personal history of drug or alcohol abuse,
- excessive caffeine (more than 150 mg/day) and alcohol (more than 250 mL/day) consumption.

Exclusion criteria of control participants will be:
- age < 18 and > 50
- inability to give an informed consent,
- presence of clinical somatic or psychiatric conditions (including sleep disorders, heart rate disorders and pathological motor activity),
- personal history of drug or alcohol abuse,
- excessive caffeine (more than 150 mg/day) and alcohol (more than 250 mL/day) consumption.

All participants will sign an informed consent prior to enrollment in the study.

3.2. Procedure
In Phase 1, all selected participants will be administered a cognitive testing session (see below). At the time of this assessment they will also be requested to complete the Beck Anxiety Inventory (BAI, Italian version, Sica & Ghisi, 2007) and the Beck Depression Inventory (BDI-II, Italian version, Sica & Ghisi, 2007) for the evaluation of anxiety and depression symptoms to be included as covariates in data analyses. Moreover, they will complete an Epworth Sleepiness Scale (ESS, Italian version, Vignatelli et al., 2003) for the assessment of habitual sleepiness levels and the SF-36 questionnaire (Italian version, Apolone & Mosconi, 1998) to evaluate health-related quality of life. Subjects will be then be required, for one week, to wear an actigraph on their non-dominant wrist and to fill in a sleep log (including questions on perceived sleep quality and features) as well as a diary of daily activities. In addition, they will be requested to complete, every day of the selected week at bedtime and upon awakening, a Visual Analog Scale for mood (VAS-mood, McCormack et al., 1988) and the Karolinska Sleepiness Scale (KSS, Akerstedt & Gillberg, 1990), as well as two Numeric Rating Scales (NRS) to evaluate levels of itch (Phan et al., 2012) and pain (McCaffery & Beebe, 1989) over the last 12 hours. On the last 2 nights of the week, participants will undergo PSG recordings at home through the Somno-Art, a new generation wearable device which has been validated against standard PSG (Thiesse et al., 2021). In Phase 2, participants of Groups A and B will be randomly assigned to one of the 3 types of intervention (CBT-I, BCT, combined CBT-I + BCT) or to the control condition (no activity), each lasting a total of 8 weeks. At the end of the intervention period (T1), as well as at the 3-months follow-up (T2), they will again be administered a testing session (including complete cognitive testing plus the administration of the PSQI, BAI, BDI-II, ESS, SF-36 and PASI only for psoriatic patients) and a week of actigraphic monitoring accompanied by the daily completion of sleep logs, diaries of daily activities, VAS-mood, KSS and NRS for itch and pain. On the last 2 nights of this week, participants will also undergo PSG recordings at home through the Somno-Art.

Cognitive testing
Cognitive testing sessions will be conducted by a licensed psychologist at the Dermatology Units. The same tests will be administered both in Phase 1 and 2: scores obtained in Phase 1 will serve as a baseline for the assessment of the effects of the intervention on cognition in Phase 2. To control for mood and sleepiness
levels, the VAS-mood and the KSS will be administered immediately before the testing session. Visuospatial memory will be investigated through the Rey–Osterrieth Complex Figure Test (ROCF; Osterrieth, 1944). Subjects are given the ROCF stimulus card, depicting a complex figure, which they are asked to copy (Copy phase). Immediately after that, the card is retrieved and subjects are required to draw the same figure (Immediate Recall phase). Finally, after a 30 minutes delay, subjects are instructed to draw the same figure again (Delayed Recall phase). Location, accuracy and organization of elements make up the final score for each phase. Verbal memory will be investigated using the Italian Alternative form of the California Verbal Learning Test II (Argento et al., 2014). In this task, the experimenter verbally reads a list of 16 items to the participant. The participant then immediately reports as many words as he can remember within 30s and the procedure is repeated 5 times. The Total Immediate Recall (TIR) score is measured by the total number of correct words reported across all 5 trials. Delayed free recall is assessed after 20 minutes. To assess procedural memory we will use the Finger Tapping Test, a motor-sequence learning task commonly used in sleep research (Cellini, 2017). Participants are required to tap numerical sequences as quickly as possible with their non-dominant hand, using a numeric keypad. Participants will perform 12 blocks, each consisting of 30 seconds of tapping followed by 30s of rest. The sequences are always displayed on the screen to decrease working memory (WM) load. The score corresponds to the total number of correct sequences per 30s from each of the 12 blocks. As for executive functioning, we will assess WM, inhibition and sustained attention through the computerized versions of the Operation Span Task (OpSpan, Wolfe et al., 2014), Go/No-Go Task (Gomez et al., 2007) and Psychomotor Vigilance Task (Wolfe et al. 2014), respectively. OpSpan is a dual-procedure test that assesses WM capacity by requiring participants to shift attention between calculating mathematical equations and remembering a word. Starting at two equations alternated with two words, participants are required to indicate whether the equations are correct and then recall the target words. The number of equations and words increase by one over each subsequent trial to increase WM load. Scores range from 0 to 20, with higher scores indicating greater WM capacity. In the Go/No-Go Task participants view a computer screen and respond to specific targets (“go”) while ignoring non-targets (“no-go”) that do not meet certain criteria. Since there are proportionally more “go” targets, the participant must inhibit the pre-potency to key-press. Increasingly difficult levels introduce new criteria for targets and non-targets. Scores are reported as percentage of correct target trials, and response time to targets. The Psychomotor Vigilance Task requires participants to fixate on a screen and respond to a visual stimulus with a key press as quickly as possible; if the key is pressed >500ms after the stimulus, it is considered a “lapse” in attention. Stimulus intervals are selected at random by the software, ranging from 2 to 10 seconds. More lapses and longer reaction times result in worse scores. When the task is performed for more than 10 minutes, as in this project, performance is considered a measure of sustained attention.

CBT-I intervention
The CBT-I intervention will consist in 8 weekly individual sessions, delivered by a therapist (a licensed psychologist specifically trained in CBT-I) through web-based 45-minute sessions. Standard CBT-I components will be used including sleep restriction, stimulus control, sleep hygiene education, relaxation and cognitive restructuring (Morin, 2004). The therapist will be trained to introduce these components in the same order to all participants.

BCT intervention
The BCT intervention will consist in 16 cognitive training sessions self-administered twice a week at bedtime (participants will be prompted by the experimenter on the days scheduled for sessions), for a total of 8 weeks. The sessions will consist in playing a slightly modified version of the word game Ruzzle (as devised in Cerasuolo et al., 2020b), in which the player has 2 min to trace on a tablet screen as many words as possible with the 16 letters available in a 4x4 grid. Subjects will be instructed to obtain the highest possible score, which depends on the number of identified words, on their length and on the use of bonus
colored letters that multiply the value of the single letter or the entire word containing it. This game is an implicit multi-componential task, in which performance improvement is based on the simultaneous acquisition and refinement of several cognitive skills (procedural motor skill and various executive functions such as verbal and spatial working memory, cognitive flexibility and strategic planning and monitoring). The training session will follow the same scheme as in Cerasuolo et al. (2020b) and it will last 40 min. During the sessions, participants will be requested to keep only their desk lamp on, their smartphones set in silent mode, and windows and doors closed to avoid external noises. Ten tablets (5 per research unit) are necessary for the project.

**Combined CBT-I + BCT**
In this condition, the two interventions will be administered during the same 8 weeks but on different weekdays (i.e., BCT sessions will be completed on separate days than those of CBT-I sessions).

**Actigraphic monitoring and PSG recordings**
Pro-diary actiwatches (CamNTech, Cambridge, UK) will be used for actigraphy. Ten (5 per research unit) are necessary for the project. The following actigraphic variables will be computed for each night of recording: Total Sleep Duration; Sleep Latency; Sleep Minutes; WASO; Mean wake episode; Sleep Efficiency; Activity mean; Activity Index; Sleep Fragmentation Index. Sleep recordings will be carried out at the participants’ homes using the Somno-Art (The Strategic Partnering Organization (PPRS), France). The participants will be able to use the device autonomously, after a brief explanation. The Somno-Art, is a new generation wearable device for classification of the stages of sleep based on the heartbeats and movements of its wearer during the night.

Classical sleep variables considered in the study will be: Total Sleep Time (TST, i.e., total amount of time, in minutes, from the first appearance of N1+N2 to final awakening), Actual Sleep Time (AST, i.e., total time spent in sleep states, in minutes), Sleep Latency (SL), Sleep Efficiency (SE, i.e., percentage of AST over TST), sleep stage proportions, percentage of Wake After Sleep Onset (WASO) over TST. Sleep quality will also be evaluated through an additional set of variables (Conte et al., 2021) indexing: a) sleep continuity: frequency of awakenings per hour of AST; frequency of brief (<4 epochs) and long (≥4 epochs) awakenings per hour of AST; frequency of awakenings from N1+N2, N3, REM sleep per minute of that stage; b) sleep stability: frequency of arousals per hour of AST (defined as all transitions to shallower NREM sleep stages and from REM sleep to N1+N2); frequency of arousals from N3, REM sleep per minute of that stage; frequency of state transitions (defined as all transitions from one state to another) per hour of TST; frequency of “functional uncertainty periods” (FU periods; defined as periods in which a minimum of 3 state transitions follow one another with no longer than 1.5 min intervals) per hour of TST; frequency of “functional uncertainty periods” (FU periods; defined as periods in which a minimum of 3 state transitions follow one another with no longer than 1.5 min intervals) per hour of TST; percentage of total time spent in FU (TFU) over TST; c) sleep organization: number of complete sleep cycles, defined as sequences of NREM and REM sleep (each lasting at least 10min) not interrupted by periods of wake longer than 2min; total time spent in cycles (TCT) over TST.

3.3. Low interventional aspect of the study
The risks for the enrolled subjects will be minimized by the eligibility criteria compliance as well as the correct execution of the study procedures. Considering that the planned study procedures consist in 3 types of cognitive functioning intervention (CBT-I, BCT, combined CBT-I + BCT versus a control condition), patients will be not subjected to any invasive interventions.

4. Working hypotheses and expected results
The main hypothesis tested in Phase 1 regards the presence of subtle microstructural sleep alterations in psoriatic patients, both with and without subjective sleep complaints. In other words, PSG-detected impairments of sleep quality can be expected to emerge in Groups A, B and C compared to controls.
Moreover, it is expected that impairments in cognitive functioning (especially in the executive domain) compared to controls parallel those in sleep measures in all three groups. No specific hypothesis on between-groups differences is made with regard to night-to-night variations in actigraphic parameters over one week; however, we expect to observe day-to-day associations of night-sleep parameters with daily measures of itch, pain, subjective sleep features and daytime activities. Similarly, associations between anxiety and depression symptoms, psoriatic symptoms severity (in the psoriatic subgroups), quality of life, objective and subjective sleep quality and cognitive functioning are predicted. As for Phase 2, all four sets of dependent variables (subjective and objective sleep measures, cognitive functioning, dermatological symptoms severity and quality of life) are expected to show improvements at T1 compared to T0 in the 3 intervention subgroups of both Group A and B, while no improvement is predicted in the control condition. The improvements in dependent variables will plausibly be greater after the combined relative to the single interventions. Similarly, it is foreseeable that the benefits observed at T1 on the different sets of parameters will be maintained at T2 in the combined intervention subgroups to a greater extent than in the single intervention groups. Instead, the comparison of treatment effects between groups (psoriatic vs non-psoriatic poor sleepers) is intended as exploratory, with no directed hypothesis.

5. Role of each research unit

The two units (University of Campania Vanvitelli and University of Firenze) will conduct the same research protocol in parallel, for the whole duration of the project, with the same instruments and specific procedures. Feasibility has mainly motivated this choice, considering the necessity to recruit a wide sample and to perform measurements of Phase 1 and interventions and measurements of Phase 2 within a limited time span. At the same time, this choice will allow us to obtain a more representative sample (coming from areas of both central and southern Italy) and more generalizable results, as well as to avoid, in data analysis, possible biases linked to geographical/cultural differences between groups which could arise if different groups were recruited in different regions. The two research units will therefore collaborate and coordinate during all phases of the project through regular web-based staff meetings, aimed to plan details of the project and create shared guidelines on their implementation, to monitor adherence to the latter guidelines, to solve potential problems and to monitor all phases of recruitment and data collection. Along the same line, a common database will be created and analyses will be conducted in parallel by the two units to ensure their accuracy. Results interpretation as well as their dissemination will also be discussed and monitored during meetings involving the whole project staff.

6. Statistical plan

6.1. Determination of the sample size

With regard to RCT (Phase 2), according to a power analysis conducted through G*Power, 21 participants per group are necessary for an effect of $2p = .04$ and 80% power (8 groups, rmANOVA with 3 measurements, alpha = .05). Therefore, 84 participants will be recruited for Groups A and B (those undergoing Phase 2), respectively. The remaining two groups (C and D), only participating in Phase 1, will be composed of at least 45 participants in order to obtain the same effect size and power according to the power analysis (4 groups, one-way between-subjects ANOVA, alpha = .05). Thus, the final sample will consist of a total of 258 participants (i.e., 45 psoriatic patients without sleep complaints, 84 psoriatic patients with sleep complaints, 84 non-clinical participants with poor sleep, 45 healthy good sleepers).

6.2. Statistical analysis

Phase 1: Objective and subjective sleep measures as well as cognitive functioning variables and the quality of life score in the four groups (A,B,C,D) will be compared by means of ANOVA (or the corresponding non-parametric statistics in case of violation of the assumptions of ANOVA). The analyses will control for potentially moderating variables (e.g. mood, sleepiness, itch and pain). To investigate the stability of sleep-
wake patterns over time, the variability of actigraphic variables will be compared across groups by means of F-statistics. Bonferroni correction will be adopted to avoid type 1 errors.

The primary endpoint for Phase 1 will be represented by measurements derived by PSG in the different subgroups of patients. Specifically, the following standard sleep variable will be analyzed: time in bed (TIB), as the number of minutes from lights-out to lights-on. The co-primary endpoint for Phase 1 will be the following actigraphy measure ‘Activity Time’ (in minutes) was computed for the 30-min window (within the 2–4 pm 2-h period) during which the patient had the highest level of 'activity', as defined above, per day, which ranged from 0 to 30 (minutes of activity per day).

Phase 2: To assess the differential effects of interventions (CBT-I, BCT, combined CBT-I + BCT, control condition) on subjective and objective sleep measures, cognitive functioning variables and quality of life score, a General Linear Model (GLM) for repeated measures with the time points of assessment as within-subjects factor (T0 ,T1, T2) and two between-subjects factors (Factor 1: interventions; Factor 2: Group A vs Group B) will be adopted. With regard to psoriatic patients, dermatological symptoms severity will be taken into account as dependent variable in a GLM with the time points of assessment as within factor and interventions as between factor. The analyses will control for potentially moderating variables (e.g., mood, sleepiness, itch and pain). Bonferroni correction will be adopted to avoid type 1 errors.

The primary endpoint for Phase 2 will be represented by measurements of the scores achieved by the Ruzzle game at the end of interventions (CBT-I, BCT, combined CBT-I + BCT).

7. Time plan and implementation

The project will develop over a two years’ time frame. During the first month, materials and instruments for data collection will be arranged in both units. Recruitment will start immediately: screening of clinical (psoriatic patients with and without sleep complaints) and non-clinical (poor sleepers and healthy controls) participants will be conducted, respectively, by the medical and psychological teams of the two units. Specifically, the screening and recruitment of the clinical sample will be performed at Dermatology Unit of University of Campania “Luigi Vanvitelli” and at the Department of Health Science, Section of Dermatology of the University of Firenze. In parallel, project staff (psychologists) of both units will advertise the study through social media and university press and perform the screening at the Sleep Labs of both universities. Recruitment will continue until the target sample size is obtained (for a maximum duration of 1 year). In fact, data collection of Phase 1 (cognitive testing + one week of actigraphic monitoring including 2 nights of sleep recording for each subject) will be started and will proceed along with recruitment. Data will be collected from maximum 20 participants per week (10 per research unit) by two experimenters per unit who will be in charge of organizing and implementing the procedure. At the same time, a third experimenter, blind to the study groups, will start the analysis of data from cognitive assessments, actigraphic recordings, daily self-report measurements and sleep recordings. Being performed progressively alongside recruitment, data collection and analysis for Phase 1 will end maximum in the 13th month of the project. The conduction of Phase 2 will also follow the progression of recruitment and of Phase 1 data collection. Therefore, each recruited participant of Groups A and B (healthy poor sleepers and psoriatic patients with complaints of poor sleep, respectively) will be randomly assigned to one of the 4 RCT arms (CBT-I, BCT, CBT-I + BCT, control condition) and will begin the 8-weeks intervention (or control condition) period consecutively, just after the end of data collection of Phase 1. Similarly, T1 data collection for each of these participants will start immediately after the 8-weeks period and T2 measurements will be collected exactly 3 months from T1. During this phase, one psychologist per unit will conduct CBT-I sessions (maximum 35 sessions per week per unit), while an experimenter per unit will be in charge of implementing and monitoring the BCT interventions. Again, two experimenters per unit will be in charge of data collection for T1 and T2, while a third, blind to the RCT arm, will analyze the data progressively as they are obtained. The whole Phase 2 (comprising the 8-weeks period of intervention or control condition, the week of T1 data collection, the 3-months interval between T1 and T2, and the week of T2 data collection) will last a total of 5.5 months for
each individual participant. Predictably, the first participants engaged in Phase 2 will start the intervention period not before the 8th month of the project and Phase 2 will be concluded for all participants within the 18th month. The final 6 months of the project will be devoted to the finalization of data analyses, to the interpretation, publication and dissemination of results.

8. Project significance
First of all, from a theoretical standpoint, in Phase 1 of the project we aim to clarify the actual impact of objective sleep disturbance in psoriatic disease. Although literature widely reports a very high prevalence of sleep disruption in individuals with this disease (Henry et al., 2016), these estimations are largely based on subjective reports (often obtained through non-validated measures; Henry et al., 2016) or on the frequent presence of comorbid diagnosed sleep disorders in psoriatic patients. Instead, a comprehensive and in-depth analysis of sleep parameters in this population is still completely lacking, as evidenced by the fact that, to this day, less than ten studies have assessed sleep objectively in psoriatic patients and these have focused on obstructive sleep apnea rather than general sleep architecture and quality (e.g., Karaca et al., 2013), have exclusively relied on actigraphy rather than polysomnography (Henry et al., 2020), or have assessed only psoriatic participants with no comparison to a control group (e.g., Papadavid et al., 2013). Therefore, our project aims to provide the first thorough description of sleep architecture and quality in psoriatic patients. Specifically, individuals with mild psoriasis will be selected, in order to explore the possible presence of subtle sleep impairments even in patients with low symptom severity, in whom the contribution of external sources of disturbance to sleep (e.g., itch, pain) is minimized. This will allow a better understanding of how sleep disturbance is linked to psoriatic disease: the observation of sleep impairments even in absence of external causes of disturbance would allow to exclude that sleep dysfunction in this pathology is merely a “secondary effect” of its symptoms (such as itch or pain) and it would rather suggest the existence of deeper links between psoriatic disease and sleep disturbance (e.g., through inflammatory pathways) To this end, the analysis of sleep will include, in addition to classical sleep quantitative variables (such as sleep onset latency, sleep duration, sleep states proportion), a set of parameters which have been shown to more accurately describe sleep quality (namely sleep continuity, stability and cyclic organization variables (Conte et al., 2021). While the latter analyses will be conducted on two nights of polysomnographic recordings, the use of actigraphy over one consecutive week, along with sleep diaries and other daily measures of functioning (e.g., bedtime sleepiness, subjective level of pain and itch at bedtime) over the same week, will also allow to obtain a profile of sleep-wake patterns and to assess factors contributing to night-to-night variations in sleep quantity and quality. The comparisons of these outcomes across four groups (psoriatic patients with sleep complaints, psoriatic patients without sleep complaints, healthy poor sleepers, healthy controls with no sleep complaints) will allow a precise characterization of sleep disturbance in psoriasis. In particular, considering that the relationships between subjective and objective sleep quality are not linear and still debated (e.g., Conte et al., 2020), it is possible that even psoriatics with no sleep complaints show subtle objective sleep impairments that affect their symptomatology and daytime functioning even though they are not consciously perceived. Moreover, the analysis of associations of subjective and objective sleep features with measures of symptom severity and daytime functioning will contribute to shed light on the bidirectional relationship between sleep dysfunction and psoriatic disease. Finally, our comprehensive assessment of cognitive performance along with its comparison between psoriatic participants, poor sleepers and good sleepers, will allow us to gauge the contribution of sleep impairment in the cognitive deficits evidenced in psoriatic samples (Colgecen et al., 2016; Marek-Jozefowicz et al., 2017; Innamorati et al., 2018). It is worth noting that obtaining a proper characterization of sleep impairment in psoriasis appears particularly important since psoriasis is independently correlated with many of the same comorbidities as sleep disruption (Shah et al., 2017). The level of risk for health related to each condition can thus compound with potentially lethal outcomes. Therefore, a clearer description of the risks associated to this condition is required to raise clinicians’ awareness and better orientate their treatment choices. In an applicative perspective, Phase 2 of
our project bears important implications for the treatment of psoriasis as well as of sleep disturbance. First of all, although CBT-I has a wide evidence base sustaining its efficacy for sleep dysfunction comorbid with several psychiatric and medical conditions (Wu et al., 2015), it has never been applied in a psoriatic sample. Of note, its administration in such a sample appears particularly promising both in light of the high prevalence of sleep disruption in this population and because the effect of CBT-I in comorbid insomnia has been found to extend to comorbid outcomes (Wu et al., 2015). Therefore, if a beneficial effect of CBT-I on sleep, psoriatic symptomatology, cognitive functioning and especially quality of life in psoriatic patients were obtained, this would open the way to the inclusion of CBT-I protocols among the viable and evidence-based non-pharmacological treatment options for dermatological care of this kind of disease. Also, such a result would encourage further research on the administration of this kind of interventions in populations with similar pathologies, e.g., atopic dermatitis. This reasoning applies all the more to our possible findings on the BCT intervention. Indeed, despite the ample data produced in sleep research on the benefits of bedtime cognitive tasks on subsequent sleep (Cerasuolo et al., 2020a), their potential application in sleep-impaired populations has not yet been systematically explored, despite the existence of encouraging results obtained on the elderly (Naylor et al., 2000; Peters et al., 2008; Haimov & Shatil, 2013) and on samples with insomnia (Haimov & Shatil, 2013) and with periodic limb movements (Sergeeva et al., 2017). Similarly, the effects obtained on sleep through these cognitive interventions have never been compared to those of standard CBT-I. Therefore, our investigation on the long-term effects of bedtime cognitive training, compared to CBT-I, represents a significant step towards clarifying the efficacy of this type of intervention in sleep-impaired individuals. It goes without saying that the use of self-administered bedtime cognitive tasks as a behavioral treatment option in pathologies such as psoriasis (and, in general, in sleep-disordered populations) could represent a very promising way to increase feasibility and compliance to non-pharmacological interventions when classical structured therapy protocols are difficult to implement. Finally, the study of psoriasis requires attention since this disease entails a relevant economic burden, especially when considering that its incidence has been found to increase across the last thirty years (AlQassimi et al., 2020): according to the National Psoriasis Association of America, these individuals lose 56 million work hours per year (Mansouri et al., 2015). Furthermore, medical costs are elevated (Pilon et al., 2019). Taking together these costs and work efficiency losses, it is estimated that the total burden of psoriasis is 35.2 billion dollars (Pilon et al., 2019). In this perspective, investigating possible low-cost and easily accessible interventions to improve health and quality of life in this population appears particularly timely.

9. Financing and insurance
9.1. Financing
The study budget will be covered by PRIN: PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE - Bando 2022, project code 2022JARZRR, entitled “Psoriasis and sleep: an integrated clinical and cognitive approach” funded by Ministero Università e Ricerca, Principal Investigator Prof. Giuseppe Argenziano.

9.2. Insurance
Given the low interventional aspect of the present study, the Principal Investigator will submit to the Ethics Committee an insurance certificate in Italian, duly executed by the insurance company under a valid insurance policy.

10. Ethics
10.1. Ethical compliance
This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:
- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable national and local laws and regulations of the pertinent regulatory authorities, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

10.2. Ethics Committee
The investigator will submit this protocol and any related documents to the local Ethics Committee (EC). Approval from the EC must be obtained before starting the study, and should be documented in a dated letter/email to the investigator, clearly identifying the trial, the documents reviewed and the date of approval. Modifications made to the protocol after receipt of the EC approval must also be submitted as amendments by the investigator to the EC in accordance with local procedures and regulations.

10.3. Informed consent procedure
A properly executed, written, informed consent form, in compliance with GCP according to International Council for Harmonisation (ICH) guidelines local regulatory requirements, and legal requirements, including applicable privacy laws, will be submitted by the investigator to the EC for review and approval prior to the start of the study. Before entering patients into the study, a copy of the EC-approved informed consent will be reviewed with the potential participant, and signed and dated. Informed consent must be obtained prior to the subject entering the study, and before any protocol-directed procedures are performed. The investigator must ensure that each study subject is fully informed about the nature, objectives and methods of the study and possible risks associated with participation. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. The investigator must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason without any prejudice. The informed consent will be provided in Italian. The investigator will provide a copy of the signed informed consent form to each patient and will maintain a copy in the patient’s study file. A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study. If a subject is unable to sign the informed consent, a legal representative may sign for the subject. Proper informed consent forms are attached as annexes to the present protocol.

10.4. Confidentiality
All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law. Subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system described above in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject’s numerical code to his or her actual identity. In case of data transfer, the Investigator will maintain high standards of confidentiality and protection of subjects’ personal data consistent with applicable privacy laws. Should direct access to medical records require a waiver or authorization separate from the subject’s signed informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

10.5. Conflict of interest
The personnel involved in the study have no conflicts of interests of any kind.

11. Study-related responsibilities and publication policy
11.1. Responsibilities
The principal investigator will be responsible for:
- Conducting the study according to the final study protocol and according to the principles of Good Clinical Practice (GCP);
- Providing the EC with all appropriate material, including the informed consent document;
- Obtaining EC approval for the proposed studies;
- Ensuring that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions;
- Maintaining a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties;
- Keeping a record of all subjects who sign an informed consent document and are screened for entry into the study;
- Providing patient clinical data associated with collected samples and a current sample inventory log.

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