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Medication review improves pain management and quality of life in chronic pain: a pilot randomized controlled study

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Chronic pain is a complex condition that benefits from a multidisciplinary approach. This pilot parallel-group single-blinded randomized controlled study evaluated the feasibility, acceptability and adherence by patients and physicians of pharmacist-led medication review on chronic pain patients. Trends in pain intensity, quality of life and patient satisfaction were examined. Twenty adults were recruited from two primary care units in Porto, Portugal, and randomly assigned to either the medication review (MR) group, ($n = 10$) using the Dader method, or the usual care (UC) group, ($n = 10$) and given general advice, for 16-weeks. Pain intensity decreased by 2.07 (MR group) and increased by 0.52 (UC group), yielding an adjusted mean difference of 2.77 (95% CI, -4.93 to -0.62; $p = 0.008$). Pain relief was reported by 62.5% in the MR group versus 37.5% in UC ($p = 0.357$). The MR group showed significant improvement in physical functioning ($p = 0.019$) and higher treatment satisfaction ($p = 0.029$). The acceptance rate of MR interventions was 71%, which resolved 63% of negative medication outcomes. Acceptability was high (> 90% of planned interviews). Conducting pharmacist-led MR for chronic pain management in primary care is feasible and well accepted by patients and physicians. Observed trends toward improved pain and QoL warrant confirmation in a larger trial. This pilot trial was registered in clinicaltrials.gov (NCT06997861).

Keywords Medication review, Chronic pain management, Primary care, Pharmaceutical care, Dader method

Abbreviations

QoL	Quality of life
MR	Medication review
DRP	Drug related problem
NOM	Negative outcome of medication
CVD	Cardiovascular disease
UC	Usual care
PCU	Primary care unit
PI	Pain intensity
NRS	Numerical rating scale
BPI	Brief pain inventory
PGIC	Patient global impression of change
BBI	Bang's blinding index
SD	Standard deviation
ITT	Intention-to-treat
PP	Per-protocol

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Chronic pain, defined as pain lasting longer than 3 months[1], is a major health and economic burden due to the profound toll it has on patient's daily activities, quality of life (QoL) and productivity[2]. A 2019 European study evaluating pain found varying prevalence rates ranging from 40% for back pain to 21% for foot/leg pain, leading authors to characterize these findings as an "European epidemic"[3]. Latest surveys report that about 20.9% of the US population has chronic pain, with 6.9% of these suffering from pain that significantly impacts daily activities[4]. Chronic pain affects roughly one in every three persons in Portugal, similar to cardiovascular disease, the leading cause of death in the country[5,6], and the use of analgesics has increased in the past years[7]. Furthermore, chronic pain is three times more prevalent than diabetes[8].

The multidimensional nature of chronic pain possesses a significant hurdle for both assessment and management. Consequently, a multidisciplinary approach is essential to optimize patients care, although pharmacological interventions still play a central role[9,10]. While effectiveness and safety of analgesics are well established, satisfactory outcomes in pain relief and QoL remains elusive. Moreover, most chronic pain patients are first managed by general practitioners in primary care settings, who demonstrate difficulties in handling these patients. Reasons for these difficulties include inadequate training, mostly related to lack of time, and reluctance in prescribing opioid analgesics, due to concerns of tolerance, dependence and side effects[11,12]. In addition, non-adherence to pharmacotherapy, characterized by the intentional or unintentional non-use or misuse of drugs, is prevalent among chronic pain patients, with rates comparable to those observed in individuals with asymptomatic pathologies[13]. Given these challenges, pharmacy-led interventions can play an important role in chronic pain management by providing specialized services and expertise in supporting primary care services.

Pharmaceutical care involves professional patient care practice with the aim of achieving medication-related outcomes by pharmacy professionals, assuming responsibility for those outcomes. Medication review (MR) is a crucial component of pharmaceutical care, consisting of systematic evaluations of patient's medications and clinical status to optimize pharmacotherapy[14,15]. In Europe, MR is commonly implemented through prescription and adherence monitoring programs, yet more advanced MR requiring patient interviews and access to clinical information remain scarce in most countries[16]. The Dader method is used to implement advanced MR in all types of settings[17]. Through ongoing patient interviews, clinical and pharmacotherapy information is gathered that allows for the development of individualized care plans, periodically adjusted to solve drug-related problems (DRP's) and negative outcomes of medication (NOM's)[18]. Randomized controlled studies, where MR using the Dader method was implemented, report significant improvement in clinical outcomes, on specific cohorts like depressed patients or cardiovascular disease (CVD) patients[19,20]. Moreover, MR interventions may have a positive impact on healthcare systems, lowering costs associated with morbidity and mortality in CVD, which translates into quality-adjusted life years[21], albeit this is not the case in all pathologies or settings[22,23]. Literature of MR, which specifically addresses chronic pain, is also limited and reveals mixed findings in pain relief and function improvement, likely due to variations in methods, settings, and MR practices[24–27]. The need for standardized MR approaches by the pharmacy professionals is vital to determine its role in the management of chronic pain. This pilot study was conducted to evaluate the feasibility of implementing pharmacist-led MR for chronic pain management in primary care using a randomized controlled trial design. Specifically, the study aimed to determine whether it was feasible to (i) conduct MR within a randomized framework (ii) ensure the acceptability of interventions among chronic pain patients and (iii) achieve adherence to the interventions by both patients and physicians. Analysis of pain intensity, QoL and patient satisfaction was also undertaken to inform the design of a future, large scale trial. This paper reports the preliminary findings from this 16-week pilot randomized controlled study, comparing MR using the Dader method to usual care (UC) in patients with non-cancerous chronic pain.

Methods

Design

This was a controlled, parallel-group, single-blinded, randomized pilot study carried out from March 2024 to June 2024, with chronic pain patients with the aim to evaluate the prospect of a larger trial design and explore the implementation of MR using the Dader method contrasted with UC. The CONSORT statement for reporting parallel group randomized studies and the 2010 CONSORT statement extension for randomised pilot and feasibility trials were applied[28,29]. The study was registered at ClinicalTrials.gov (NCT06997861; 30/05/2025). The protocol was predefined and implemented as planned.

Ethics approval

The research protocol was approved by the ethics committee of the North Regional Health Administration, under the jurisdiction of the Portuguese Health Ministry (record nº CE/2023/87). The study adhered to the principles of the Declaration of Helsinki and participants provided written consent before study entry.

Participants

Participants recruitment took place in two primary care units (PCU's) in Porto, Portugal managed by ACeS Porto Oriental (USF Arca D´Água and USF Campanhã - Polo S. Roque da Lameira). Eligibility criteria for enrollment were: age between 18 and 70 years; non-cancerous chronic pain (persistent or recurrent pain for longer than 3 months), regardless of etiology; followed-up in one of the aforementioned primary care setting; having a weekly average pain intensity (PI) score of at least 4 or more points on an 11-point numeric rating scale (NRS) at screening phase; ability to commute to our research center for monthly interviews or meet via video meeting platforms. Participants were excluded if they were pregnant, breastfeeding or presented with a diagnosis of dementia or other mental disease hindering the ability to self-report. As "chronic pain" is not a diagnostic label, the selection strategy involved generating lists of patients labeled with specific codes from the PCU's software, linked to clinical records from consultations. This increased the likelihood of identifying a patient

suffering from pain lasting at least 3 months (e.g., L89 - hip osteoarthrosis; L90 – knee osteoarthrosis; A01 – generalized/multiple pain). These lists were then compiled with the help of PCU's coordinators between August and October 2023 and included patients who had attended consultations in the previous 3 months. From these lists, 80 patients were randomly selected using Microsoft Excel®. The main investigator contacted these patients via email or telephone, applying a brief questionnaire verbally or in writing to access eligibility (screening phase). Eligible patients were then invited to participate, and informed consent was obtained.

Interventions

Participants were randomly assigned in a 1:1 ratio to either the MR group (MR, $n = 10$) or the UC group (UC, $n = 10$) for a 16-week study period. Block randomization with a block size of 2 was used, matching for sex and age to ensure a uniform distribution of men and women of similar ages in each group. Allocation to each arm was conducted using random computer-generated numbers attributed to each block, allowing for a random and evenly distributed sample. The randomization sequence was generated by the study main investigator who also enrolled participants as stated above. Group assignments were carried out by another researcher using sequentially numbered, sealed opaque envelopes. Blinding was maintained, as participants were unaware of the type of intervention they would receive; they were only informed that they would have monthly interviews aimed at helping reduce their pain, conducted by one of the investigators trained in MR. To further reduce chances of bias, interviews were similar in both groups. The interviews held at the investigation center REQUIMTE, School of Health – Polytechnic Institute of Porto.

Medication review group

According to the Pharmaceutical Care Network Europe's definition, the MR group was provided with type 3 MR which involves obtaining and analyzing medication history, patient information and clinical information, using the Dader method[17,30]. Briefly, the Dader method was delivered in four phases:

1. Study phase: face-to-face interviews were conducted to record participants' health problems and pharmacotherapy. The patients gave information on medication history, main complaint regarding pain (e.g. low back pain, osteoarthritis, migraines) and other comorbidities. Anthropometric measurements and other information (e.g. lifestyle, smoking habits, diet habits) was recorded if deemed necessary.
2. Assessment phase: Evaluation of pharmacotherapy was performed to identify DRP's and NOM's. For each health problem the investigator evaluated if the medication was necessary, safe and effective. In practice this may involve for example, identifying the use of suboptimal doses of analgesics.
3. Intervention phase: Individualized care plans were developed. These plans include measures aimed at physicians (e.g., medication adding; dose reduction) and patients (e.g., non-pharmacological measures; adherence to medication). For instance, reports were sent by email to physicians with requests to add/remove medication or modify doses.
4. Follow-up phase: Follow-up interviews were conducted to assess care plans results and the need for therapeutic adjustments. All MR group participants received four face-to-face interviews (Fig. 1). The first interview involved gathering information related to participants' health problems and pharmacotherapy (study phase). The second interview, a care plan on paper was delivered to participants and reports were sent to physicians if necessary (intervention phase). The third interview assessed results and adjusted care plans (follow-up phase). The fourth interview evaluated the outcomes, the need for therapeutic adjustments and concluded the trial.

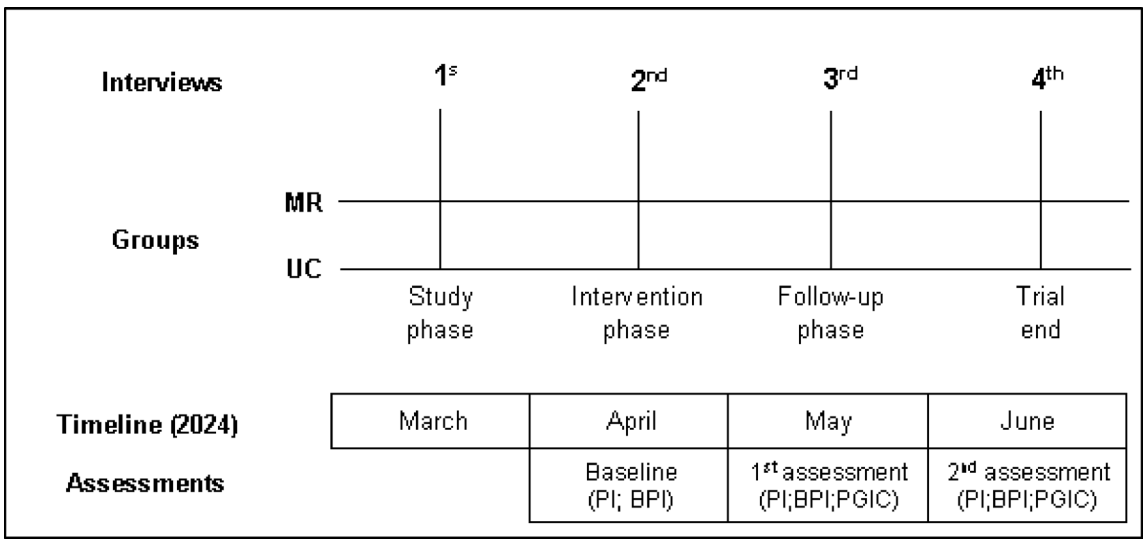

Fig. 1. Illustration of study design. MR: Medication Review; UC: Usual Care; PI: Weekly Average of Pain Intensity; BPI: Brief Pain Inventory interference scale; PGIC: Patient Global Impression of Change.

Usual care group

The UC group also received a total of four face to face interviews (Fig. 1), including follow-ups, similar to the MR group. Information gathered was used only to provide general advice on how to manage their pain and/or recommendations to take "over the counter" drugs, similar to community pharmacy visits. These interventions were delivered verbally and on paper. No new advice or recommendations were given in follow-ups, although verbal reinforcement of previously given information was provided.

Primary and secondary outcome measures

Three main indicators were defined to assess the feasibility of conducting a larger trial:

1. Trial design feasibility: evaluated by the relative frequency of identified and resolved NOMs.
2. Participants acceptability: assessed using the relative frequency of planned versus conducted interviews.
3. Adherence to interventions: estimated from the relative frequency of proposed versus implemented interventions by both participants and physicians.

The primary outcome was the reduction in weekly pain intensity from baseline to week 16 on an 11-point NRS scale with descriptors, where "0" is "no pain"; 5 is "moderate pain" and 10 is "the worst pain imaginable". PI was defined as the mean of three measurements taken on Monday, Wednesday and Friday. Participants were instructed to select which best describes the pain they felt in the last 24 h and record their score in the morning. Furthermore, participants were instructed to record their pain scores seven days prior to each scheduled interview. In line with IMMPACT guidelines, the study also reported "responder status", defined as the proportion of participants achieving a "minimally important" reduction (between 10 and 20%), "clinically meaningful" reduction (≥ 30%) and a "highly meaningful" reduction (≥ 50%) in PI from baseline to week 16[31].

Secondary outcomes included physical functioning, measured by the interference scale of the Brief Pain Inventory (BPI) and global improvement and satisfaction with treatment, measured by the Patient Global Impression of Change (PGIC)[32,33]. Treatment success was defined by score 5 (moderately improved), score 6 (much improved) and score 7 (very much improved) of the PGIC scale at week 16. Baseline measurements for primary and secondary outcomes except PGIC were taken the week before the second interview. Outcome assessments were conducted the week before the third and fourth interviews (Fig. 1). All outcomes were self-reported.

Blinding assessment

Blinding was assessed at the end of the study in the last interview, before participants were informed of the study results. Participants were asked to guess which group they were allocated to (MR or UC). If the participants were uncertain about their allocation their response was registered as "don't know". Bang's Blinding Index (BBI) was calculated to quantify the success of the blinding procedure. The BBI ranges from − 1 to 1, with 0 indicating perfect blinding, positive values suggesting unblinding toward the treatment group, and negative values indicating unblinding toward the placebo group[34].

Statistical analysis

The sample size was estimated to detect a difference of 2 points in the NRS scale for PI between groups from baseline to week 16, with 80% power and a significance level of 0.05. Using a two-sided test, a sample size of 17 participants was required. The specified effect size represents a "meaningful" decrease in PI, consistent with reductions in pain of 30% to 36%, and is the proposed benchmark for clinical trials reporting PI[35]. The chosen effect size is based on the fact that the sample was retrieved from the Portuguese population, where a reported average median PI of 5 with an interquatile range from 4 (25th percentile) to 6 (75th percentile) would represent a 33% to 50% decrease in PI. The 2-point effect size in our study thus exceeds the threshold for clinical significance. A standard deviation (SD) estimates of 1.48 was determined from the interquartile range for the average median PI assessed on a NRS scale in a nationwide study on chronic pain in Portugal[6] using the recommended estimator for large sample sizes[36]. To account for 15% dropout rate, the sample was increased to 20 participants, allowing for 10 participants in each group.

An intention-to-treat (ITT) analysis was conducted, including all randomized participants in the efficacy estimations if at least baseline assessment was undertaken. For continuous variables, data were evaluated using a general linear model of repeated measures Analysis of Covariance (ANCOVA), with interviews as the within-subjects factor and interventions as the between-subjects factor. Baseline scores, and body mass index (BMI; ≤25 or > 25) were included as covariates. ANCOVA assumptions were evaluated separately for the datasets of both the primary outcome and physical functioning, one of the secondary outcomes, including tests for normality, homogeneity of variance, homogeneity of regression slopes, linearity, and multicollinearity. Normality of residuals was assessed using the Shapiro–Wilk test and visual inspection of Q–Q plots. Homogeneity of variances was tested using Levene's test. The assumption of homogeneity of regression slopes was evaluated and a non-significant interaction between each covariate and the independent variable was met. Linearity between each covariate and dependent variable was verified through scatterplots. Variance inflation factors values indicated no multicollinearity between covariates. Missing data was imputed using the "last observation carried forward" approach and sensitivity analysis was performed for the primary outcome on the ITT complete case population and per-protocol (PP) population. Dichotomic outcomes (responder status and satisfaction with treatment) were compared between groups using Fisher's exact test. All values are presented as means and SD, unless stated otherwise. A P-value < 0.05 was considered statistically significant for a unilateral test. Statistical analysis was performed using SPSS for Windows version 29.0 (SPSS Inc., Chicago, IL, USA).

Results

Participants

Participant's recruitment took place between November 2023 and February 2024. A total of 80 patients from the two PCU's were screened, and 20 eligible participants were enrolled and later allocated into two groups (Fig. 2). Two of the randomly assigned participants did not receive interventions, since one of them refused to participate and the other missed baseline data, therefore we included 18 participants in the ITT analysis, with 9 in the MR group and 9 in the UC group. A total of 72 face to face interviews were planned (36 in each group) and 70 were conducted (97%); 36 in MR group (100%) and 34 in the UC group (94%). In accordance with the Dader method's monitoring procedures, no adverse events related to the interventions were reported by participants during the study or at follow-up interviews. Baseline characteristics of the participants are shown in Table 1 and are comparable between the two groups. Additionally, a summary of the pharmacological groups identified during the interviews is available in suplementary Table S1. Non steroidal anti-inflammatory drugs and paracetamol were the most used drug classes followed by weak opioid analgesics. The distribution of pharamacological groups was broadly similar between groups.

Primary outcome

At baseline,, pain scores were 6.18 ± 2.25 for the MR group and 5.82 ± 2.32 in the UC group. At week 16, the MR group's pain score decreased to 4.11 ± 2.95, while the UC group's score increased to 6.33 ± 2.87. PI decreased by 2.07 ± 3.31 points in the MR group but increased by 0.52 ± 1.90 points in the UC group, yielding an adjusted between-group difference of -2.77 (95% CI, -4.93 to -0.62; $p = 0.008$) as shown in Table 2.

In Table 3, the responder status at the end of the study is reported, showing the proportion of participants achieving varying degrees of pain reduction. At week 16, three (60.0%) participants in the MR group achieved a pain reduction of 50% or more, while none (0%) in the UC group reached this threshold. One participant in the MR group (20.0%) and one in the UC group (33.3%) achieved a pain reduction of 30%. Additionally, two participants in the UC group (66.7%) experienced a 10–20% reduction in pain, compared to one participant in the MR group (20.0%). Considering all responders, 62.5% of them in the MR group experienced some level of pain reduction, versus 37.5% in the UC group. However, the difference was not statistically significant ($p = 0.357$).

Secondary outcomes

The total pain interference score (sum of all 7 items from the BPI interference subscale) at baseline was 35.67 ± 17.85 in the MR group, and 31 ± 19.13 in the UC group. At week 16, pain interference score in the MR group decreased to 23.33 ± 16.57 and in the UC group increased to 36.33 ± 23.92. The reported adjusted between-group difference of -17.79 points (95%CI, -34.46 to 1.14; $p = 0.019$) indicates a significantly greater reduction in total pain interference in the MR group, compared to the UC group (see Table 2).

According to the PGIC scale, five participants (55.6%) in the MR group achieved treatment success, while none of the participants of the UC group (0%) reported significant satisfaction with their treatment. This difference was statistically significant ($p = 0.029$; Table 4).

At the end of the study, a total of 19 pain-related NOM's were detected, of which 12 (63%) were resolved (see Fig. 3). The most frequently identified NOM was "untreated health problem", accounting for 10 cases (52.6%). This was followed by 5 cases (26.3%) of "non-quantitative ineffectiveness", 2 cases (10.5%) of "non-quantitative unsafe" and 1 case each (5.3%) of "effect of medication unnecessary" and "quantitative unsafe". Among the individual NOM's, 6 out of the 10 "untreated health problem" (60%) cases were solved. Additionally, MR interventions successfully addressed 2 out of the 5 "non-quantitative ineffectiveness" (40%) cases. All other identified NOM's were fully resolved (100%). In Fig. 4, the type and frequency of pain-related pharmaceutical interventions according to the Dader method are presented. A total of 28 interventions were recorded. Adding a medication accounted for 10 interventions (35.7%), non-pharmacological advice was given 7 times (25%) and medication withdrawal occurred 5 times (17.9%), which constitutes the majority of performed interventions (78.6%). Additionally, there were 2 interventions each (7.1%) related to education on use and medicine administration and schedule modification. The remaining interventions included modification and medication substitution each occurring once (3.6%). Considering interventions individually, adding medication was implemented 6 out of 10 times (60%), non-pharmacological advice was implemented in 5 out of 7 times (71%) and medication withdrawal 4 out of 5 times (80%), with the remaining interventions being fully implemented (100%), except for medication substitution which was refused by the physician when suggested (100%). Overall, a total of 20 out of 28 interventions were accepted (71.4%).

Sensitivity analysis

Sensitivity analysis was conducted using both the ITT complete case and PP approaches. In the ITT complete case population, a significant reduction in pain was observed in MR group, compared to the UC group (adjusted between-group difference, -3.14; 95% CI, -5.34 to -0.94; $p = 0.009$). The PP population analysis showed a similarly significant adjusted between-group difference of -3.36 (95% CI, -5.87 to -0.86; $p = 0.013$), which is consistent with the ITT complete case findings. Both analyses confirm the results of the primary ITT analysis, underscoring the robustness of our results.

Blinding assessment

Blinding was assessed using BBI. The calculated value for the MR group was 0.625 (CI: 0.14 to 1.10) indicating a significant degree of unblinding, as participants in this group were able to guess their allocation more accurately. In contrast, the BBI for the UC group was – 0.14 (95% CI: -0.76 to 0.47), suggesting that blinding was successful in this group, with minimal ability to guess the allocation correctly.

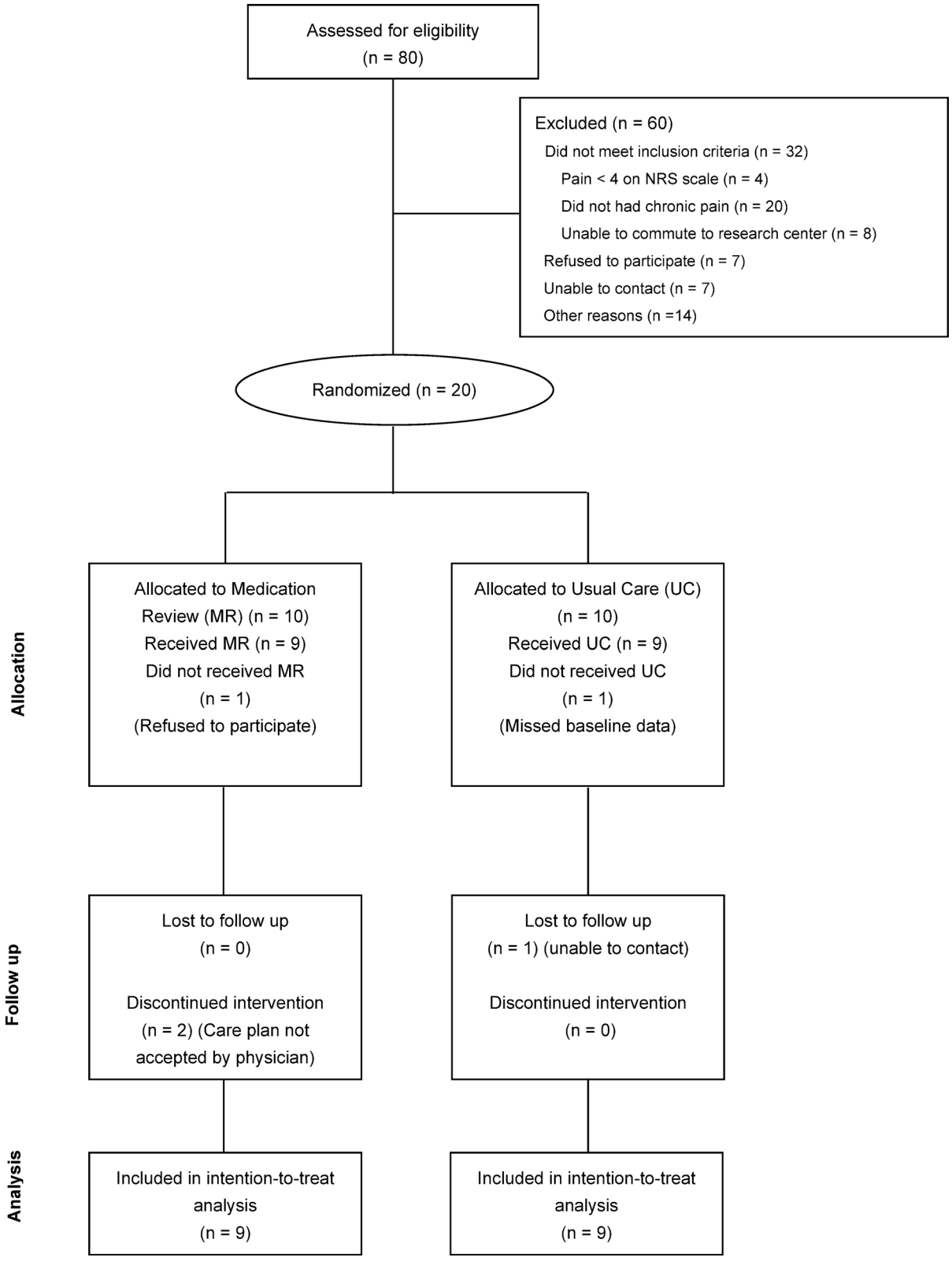

Fig. 2. CONSORT diagram. NRS: Numerical Rating Scale; MR: Medication Review; UC: Usual Care.

Discussion

The results from this parallel-group, single-blinded, pilot randomized controlled study suggest a reduction in pain in participants from the primary care setting, receiving MR using the Dader method. Pain relief was achieved following the initial intervention and sustained through week 16. Moreover, improved physical functioning

	Group	
	MR ($n=9$)	UC ($n=9$)
Age (years), mean ± SD	54 ± 8	57 ± 9
Women (%)	7 (77.87)	8 (88.9)
Education level		
Basic	4 (44.4)	4 (44.4)
Secondary	2 (22.2)	2 (22.2)
Higher	3 (33.3)	3 (33.3)
BMI > 25 (kg/m^2)	5 (55.6)	4 (44.4)
NRS pain score at baseline (0–10 points), mean ± SD	6.18 ± 2.25	5.82 ± 2.32
Pain location		
Neck	3 (33.3)	4 (44.4)
Back	3 (33.3)	4 (44.4)
Limbs	11 (57.9)	7 (77.8)
Other	2 (22.2)	1 (11.1)

Table 1. Participants baseline characteristics by group. Data are presented as No (%) unless stated otherwise. Pain type is based on patient reported symptoms and may be more than one for each patient. MR: Medication Review; UC: Usual Care; SD: Standard Deviation; NRS: Numerical Rating Scale; BMI: Body Mass Index.

Outcome	Baseline		16 weeks		Change from baseline		Mean difference* (CI 95%)	p^a
	MR ($n=9$)	UC ($n=9$)	MR ($n=9$)	UC ($n=9$)	MR ($n=9$)	UC ($n=9$)		
Primary								
Pain score NRS	**6.18 (2.25)**	**5.82 (2.32)**	**4.11 (2.95)**	**6.33 (2.87)**	**2.07 (3.31)**	**-0.52 (1.90)**	**-2.77 (-4.93 to -0.62)**	**0.008**
Secondary								
Interference (BPI)[b]								
General activity	6.11 (2.42)	5.22 (2.91)	4.44 (3.24)	6.11 (3.02)	1.67 (3.81)	-0.89 (2.57)	-2.67 (-5.22 to -0.13)	**0.021**
Mood	6.56 (3.21)	4.44 (3.05)	3.78 (3.27)	5.56 (3.47)	2.78 (3.42)	-1.11 (3.66)	-3.30 (-5.97 to -0.63)	**0.001**
Walking ability	3.11 (3.98)	5.89 (3.41)	2.44 (2.74)	5.78 (3.70)	0.67 (3.94)	0.11 (2.80)	-2.75 (-5.39 to -0.11)	**0.021**
Work	6.44 (2.29)	5.33 (3.24)	4.44 (3.21)	6.78 (3.67)	2.00 (3.46)	-1.45 (3.24)	-3.17 (-6.04 to -0.30)	**0.017**
Social relations	3.22 (3.35)	3.44 (3.09)	2.33 (2.06)	3.89 (4.43)	0.89 (3.82)	-0.45 (3.39)	-1.91 (-4.32 to 0.50)	0.055
Sleep	4.67 (3.43)	3.78 (3.83)	3.00 (2.74)	4.89 (4.11)	1.67 (3.54)	-1.11 (3.02)	-3.06 (-5.36 to -0.49)	**0.012**
Life enjoyment	5.56 (3.50)	2.89 (4.17)	2.89 (3.14)	3.33 (4.39)	2.67 (4.74)	-0.44 (4.45)	-3.06 (-5.63 to -0.49)	**0.012**
Total pain interference BPI (summed score)[b]	**35.67(17.85)**	**31.00 (19.13)**	**23.33(16.57)**	**36.33 (23.92)**	**12.33 (24.11)**	**-5.33(18.31)**	**-17.79 (-34.46 to 1.14)**	**0.019**

Table 2. NRS pain scores and BPI interference scores (Intention-To-Treat analysis). Data is given as mean (SD). *Mean difference was calculated using the analysis of covariance, adjusted for baseline scores and body mass index (< 25 kg/m^2 or ≥ 25 kg/m^2). [a]*P* values presented are for a one-tailed test. P-values indicating statistical significance (<0.05) are highlighted in bold. [b]Score ranges on subscale interference items (BPI): 0–10. Score ranges on total pain interference: 0–70. Higher scores represent increased interference with physical functioning. NRS: Numerical Rating Scale; BPI: Brief Pain Inventory; MR: Medication Review; UC: Usual Care; CI: Confidence Interval. Significant values are in bold.

and decreased functional interference was higher in the MR group compared to the UC group, resulting in a higher QoL. Additionally, the MR group reported higher treatment success and greater satisfaction with their interventions, and the completion rate of planned interviews approached 100%, indicating high acceptability of the intervention among participants.

Although literature regarding pharmacist-led interventions in chronic pain patients is limited, a trend seems to favor the pharmacy professional role. Importantly, trials where MR was applied in chronic pain patients vary in methodology, outcomes, population and settings, making comparisons difficult. To our knowledge, this is the first study, using an "RCT design" to implement MR using the Dader method specifically for chronic pain patients in a primary care setting. The Dader method uses a systematic approach that allows the pharmacist to develop specific interventions regarding the patient's pharmacotherapy and is adaptable to any setting. Of note, this study was conducted with Portuguese patients, which have one of the highest rates of chronic pain in Europe and increased use of opioids in the last 10 years[7], further highlighting the need for pharmacist-led interventions.

In our study, a total of 19 NOMS were identified of which more than half were resolved. This findings suggest that implementing MR in chronic pain patients in primary care is feasible and contribute to optimizing pharmacotherapy management. Exploratory analysis of outcomes reveal that patients in the MR group experienced a reduction in pain intensity from baseline, by 2.07 points. In contrast, the UC group's pain intensity

Pain reduction, No. (%)				
Group	**10–20%**	**≥30%**	**≥50%**	**Total**
MR ($n=5$)	1 (20.0)	1 (20.0)	3 (60.0)	5 (100)
UC ($n=3$)	2 (66.7)	1 (33.3)	0 (0)	3 (100)
Total ($n=8$)	3 (37.5)	2 (25.0)	3 (37.5)	8 (100)

Table 3. Responder status at 16 weeks, based on weekly mean numerical rating scale score. Responder Status is defined as the proportion of participants with reductions in pain between baseline and week 16 of 10–20% (minimally important), ≥30% (clinically meaningful) and ≥50% (highly meaningful). $p=0.357$ (Fisher's exact test).

Group	Success, No. (%)	No success, No. (%)	Total, No. (%)
MR ($n=9$)	5 (55.6)	4 (44.4)	9 (100)
UC ($n=8$)	0 (0)	8 (100)	8 (100)
Total ($n=17$)	5 (29.4)	12 (70.6)	17 (100)

Table 4. Treatment Success, measured by the PGIC scale. Treatment success is defined as scoring 5 (moderately improved), 6 (much improved) or 7 (very much improved) in the PGIC scale. $p=0.029$ (Fisher's exact test).

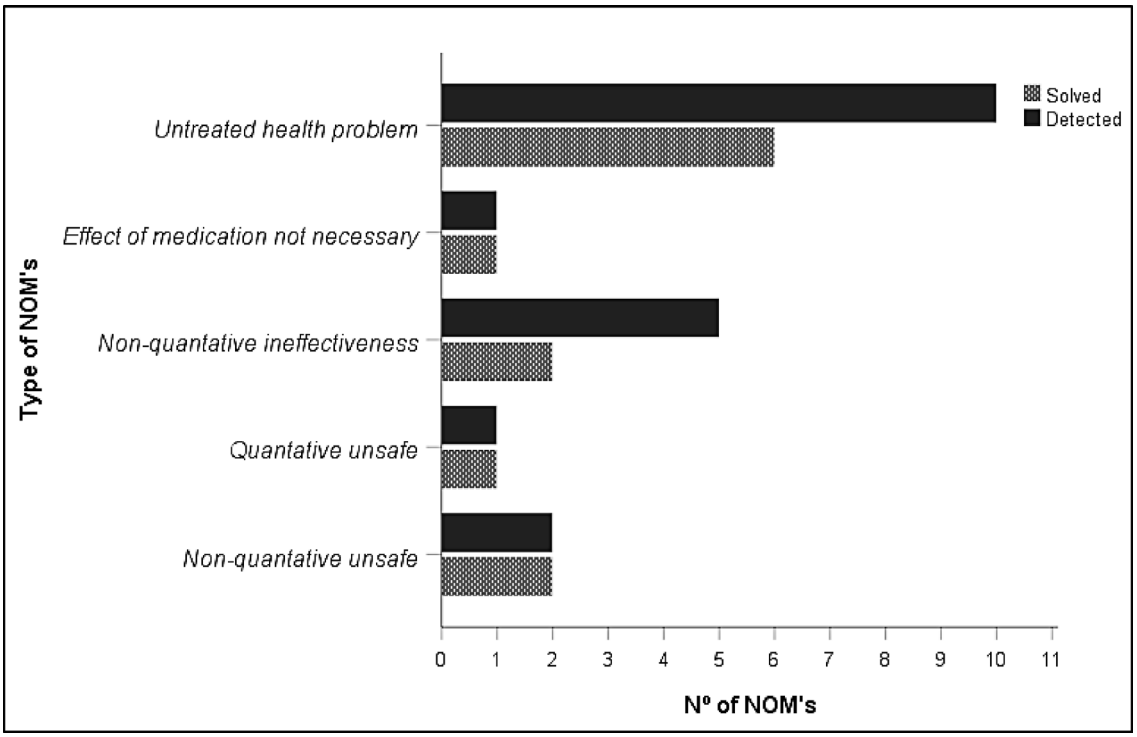

Fig. 3. Number of pain-related Negative Outcomes of Medication (NOM's) detected and solved in the Medication Review (MR) group. NOM's were identified according to the Dader Method classification.

increased by 0.52 points, yielding an effect size of 2.77 points (Table 2). This increase in the UC group, although not meaningfull, may have resulted from participants not following the general advice given to them or even by self-report bias. These results may anticipate a meaningful pain relief in the MR group, exceeding the IMMPACT recommended 2-point reduction on the 11-point NRS scale, even if we do not consider the increase in the UC group and overall effect size[35]. In a research clinical trial by Hay et al., "enhanced pharmacy review" based on a pre-defined algorithm was employed in a cohort of patients aged 55 years or older presenting with knee pain in primary care[37]. Pain scores decreased significantly between the "enhanced pharmacy review" group and the control group in three months. Similarly, Bruhn et al., implemented a pharmacist medication review with and without pharmacist prescribing in chronic pain patients, comparing these with standard care in six general

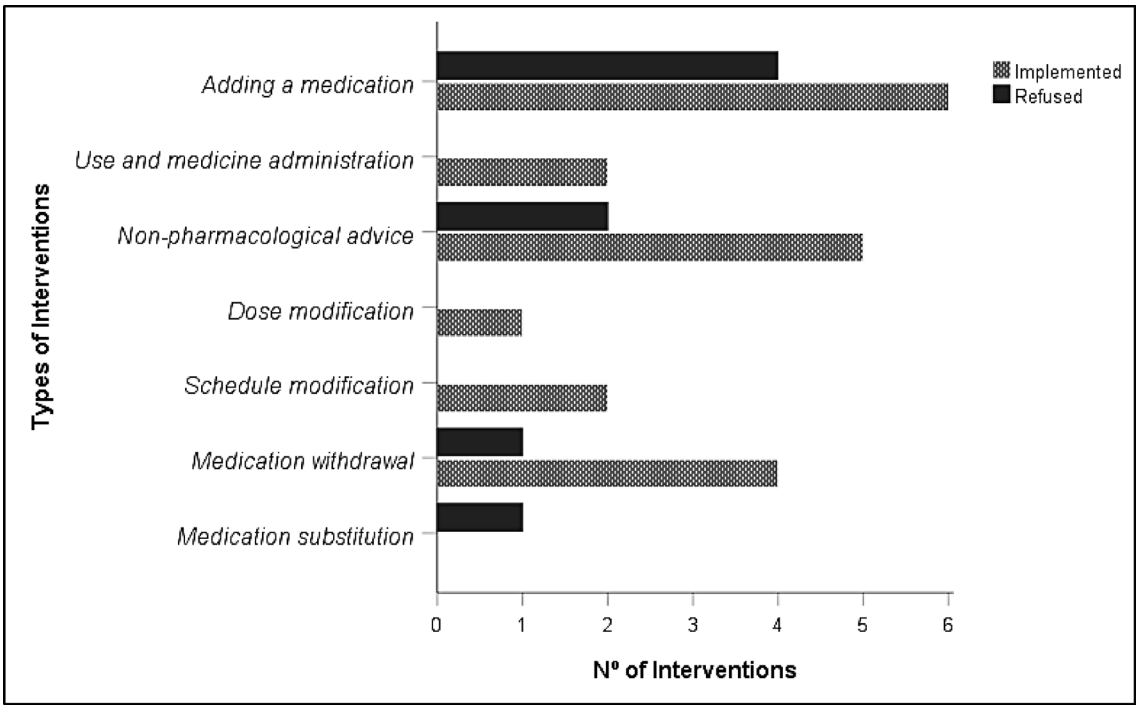

Fig. 4. Number of pain-related interventions, implemented and refused in the Medication Review (MR) group, according to the Dader Method. Interventions include recommended pharmacological and non-pharmacological strategies.

practices. Patients' pain scores improved significantly in both the prescribing arm and medication review only arm, compared to baseline and standard care at 6 months[38]. Of note, these studies used different metrics for pain and other outcomes, thus cannot be directly compared to our study. They also do not report "responder status", a necessary measurement to provide a clearer picture of pain improvement when comparing groups. By reporting responder status, our study provides a more nuanced understanding of pain improvement compared to prior studies. In our study, "responders" were defined as patients with pain relief of 10–20%; ≥30% and ≥ 50%. More than half of all the responders (62.5%) achieved some level of pain reduction in the MR group compared to 37.5% in the UC group (Table 3). Notably, among the patients in the MR group who experienced pain reduction, 60% achieved more than 50% (highly meaningful) pain reduction while none in the UC group, reached this level. These findings support a trend favoring MR implementation, although the difference was not statistically significant, which can be explained by the small sample size of the subgroup of responders (8 patients), for proportion comparisons.

Chronic pain often co-occurs with depression and anxiety, with evidence linking pain severity to these conditions[39]. Pain also impairs physical function, sleep, work productivity, and life enjoyment, significantly reducing QoL[40]. To assess intervention impact on QoL, we analyzed pain interference using the BPI scale. All domains improved significantly except social relations, which showed a non-significant but favorable trend for MR. Overall, MR significantly reduced pain interference, with a mean effect size difference of 17.79 points (Table 2). Additionally, treatment success, including patient satisfaction, was exclusively observed in the MR group (Table 4). These findings align with previous studies, which also reported improvements in physical functioning, mental health and satisfaction, using pharmacist led interventions[26,38], underscoring the value proposition of MR in enhancing QoL among patients with pain.

Physician acceptance of pharmacist MR interventions varies widely. Zaal et al. reported a 71% acceptance rate, driven by the clinical relevance of DRPs and verbal communication with physicians[41]. In contrast, Falcão et al. reported 53%, attributing the lower rate to limited verbal communication[42]. Both studies took place in hospitals, where pharmacists are often part of multidisciplinary teams, likely improving acceptance. In our study, 71% of MR interventions, primarily involving medication adjustments (addition or withdrawal) and non-pharmacological advice, were accepted, indicating higher than expected adherence by physicians, suggesting that this approach could be feasible for implementation in a larger-scale study. Our acceptance rate was comparable to the studies mentioned, although our MR reports were communicated via written emails rather than direct interaction with physicians. This setting, more akin to community pharmacy, typically experiences lower acceptance rates compared to hospital environments[43]. Lastly, adherence to care plans was monitored during each follow-up interview and through direct contacts with participants via telephone, email and messaging. This consistent engagement with participant's proved to be a usefull strategy that could be adopted in a larger trial, as it enhances patient adherence and likely contributed to improved outcomes observed in the MR group.

The "trial" approach of our study is one of its strengths, since it allowed for direct comparison between the MR group and the UC group. Moreover, the outcomes measures were consistent with the IMMPACT

recommendations for chronic pain, namely pain intensity, physical functioning, emotional functioning and global satisfaction with treatment, ensuring a complete appraisal of the interventions. The CONSORT recommendations were also followed to ensure thorough report of all the trial procedures. Unlike similar studies that either did not blind participants or failed to evaluate blinding effectiveness, we measured blinding success. While blinding was successful in the UC, more than half of the participants in the MR group accurately guessed their allocation. This raises the possibility of behavioral change (e.g. higher than expected adhesion to the care plan) in these participants which may have influenced our results. Despite the robustness of our trial, some limitations must be acknowledged. First, we cannot exclude the possibility of confounders related to unmentioned co-interventions by other healthcare professionals, other than primary care physicians, albeit no such interventions were reported by participants. Self-reported outcomes, while capturing subjective experiences of pain and physical interference, may increase the risk of measurement bias. Self-reported data may also be affected by social desirability bias or recall bias. In our study social desirability bias might have happened due to participants willingness to demonstrate they have followed the individual care plan. Recall bias also likely occurred since participants had to record the PI of the last 24 h. Another limitation of our study was its sample size, which was insufficient to detect meaningful differences in "responder status", an outcome that contributes to a more comprehensive understanding of absolute changes in pain intensity. Finally, we cannot confirm the effectiveness of interventions beyond the 16-week trial period. It is important to highlight that pharmacist-led interventions in pain management have been shown to be effective in reducing pain intensity and improving patient satisfaction. However the higher costs associated with these practices compared to usual care may present a challenge in long-term viability[44]. Future research should address these limitations by incorporating larger sample sizes and extending follow-up assessments to capture long-term effects, evaluate sustainability, and enhance the reliability of findings.

Conclusion

In conclusion, this pilot study provides preliminary evidence that pharmacist-led MR may improve treatment outcomes compared to UC in Portuguese primary care patients with chronic pain. MR was associated with trends toward reduced pain intensity, improved QoL and high levels of patient satisfaction, supporting the feasibility and acceptability of MR implementation in this context. A larger, more powered trial is warranted to confirm these initial findings and to furhter evaluate clinical effectiveness .

Data availability

The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author upon reasonable request. Individual de-identified participant data (including data dictionaries) will be made available. The following data will be shared: baseline characteristics, primary and secondary outcome measures. Additional documents, including the study protocol and informed consent form, will also be available. Data will become available beginning 6 months after publication and will remain available for 4 years. Access will be granted to researchers whose proposed use of the data has been approved by an independent review committee (data access committee) identified for this purpose. To gain access, requestors will need to submit a methodologically sound proposal outlining the purpose and analysis plan. Data will be shared under a data use agreement. Requests may be directed to the principal investigator (nsd@ess.ipp.pt).

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Author contributions

Conceptualization, JAGP and MS; Data curation, ND and JM; Formal analysis, ND, JM and MS; Funding acquisition, MGD, JAGP and MS; Methodology, ND; Supervision, JAGP and MS; Writing—original draft, ND, JAGP and MS; Writing—review & editing, ND, JM, MGD, JAGP and MS. All authors read and approved of the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Informed consent

Informed consent was obtained from all subjects involved in the study.

Institutional review board

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the North Regional Health Administration, under the jurisdiction of the Portuguese Health Ministry, record nº CE/2023/87 in September 2023.

Additional information

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