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ORIGINAL RESEARCH ARTICLE

Effectiveness of a Collaborative Deprescribing Intervention of Proton Pump Inhibitors on Community-Dwelling Older Adults: The C-SENIoR Pragmatic Non-randomised Controlled Trial

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Abstract

Background Proton pump inhibitors (PPIs) are commonly used and often prescribed inappropriately, which increases the risk of adverse events. Deprescribing is a health professional-supervised intervention aimed at reducing or discontinuing medications that may cause harm or no longer provide benefits.

Objective To evaluate the effectiveness of a collaborative intervention involving community pharmacists and general practitioners in deprescribing inappropriate PPIs (ATC/WHO A02BC) among community-dwelling older adults (aged ≥ 65 years).

Methods This was a pragmatic, multicentre, non-randomised two-arm-controlled trial with 6-month follow-up in Portuguese primary care, involving community pharmacies and family health units (FHUs) to deprescribe long-term PPIs (> 8 weeks). The intervention comprised a pharmacy-based patient awareness and education approach, followed by a clinical assessment by general practitioners to assess inappropriate use and initiate the deprescribing process, along with pharmacy-based follow-up to monitor the withdrawal process. The comparator was usual care. The primary outcome was successful deprescribing, defined as the discontinuation or dose reduction of any PPI at 3 and 6 months. Secondary measurements included clinical and drug-specific outcomes. An intention-to-treat analysis was performed.

Results The study included 166 patients (mean age 74.2 years (SD 6.0 years), 59.0% female) who had been using PPIs for an average of 10.6 years (SD 7.3 years). The intervention was found to be effective in reducing PPIs use. At 3 months, the adjusted absolute risk difference in deprescribing between the intervention group (IG) and the control group (CG) was 46.3% (95% confidence interval (CI) 32.8-59.9, number needed to treat of 2.2). The relative risk of deprescribing in the IG compared with the CG was 9.6 (95% CI 3.6–25.6). At the 6-month follow-up, the effect remained similar. No significant differences between the IG and CG were observed for secondary outcomes.

Conclusions This collaborative deprescribing intervention has been effective in reducing inappropriate PPI use, highlighting the need for ongoing multidisciplinary efforts and supportive policies to optimise medication use in older adults. Larger trials with longer follow-ups are necessary for a better assessment of various patient-reported outcomes and the long-term impact of these deprescribing interventions.

Clinical Trial Registration ISRCTN49637686, 14/06/2023 "retrospectively registered".

1 Introduction

Proton pump inhibitors (PPIs) are one of the most used classes of medications and are often prescribed inappropriately [1]. With some exceptions, clinical guidelines recommend that treatments should be given at the lowest effective dose and for the minimum period (4–8 weeks) of time [2–4]. While short-term use of PPI appears relatively safe, long-term use is associated with an increased risk of several potentially severe adverse events, including pneumonia, bone fractures and chronic kidney disease, which can significantly impact patients' health and quality of life [5, 6]. Alarmingly, studies estimate that 40–85% of individuals prescribed PPIs lack a justified indication for prolonged therapy, raising concerns about the potential harms associated with inappropriate use [1, 7]. In Portugal, a cross-sectional study by Simões et al., involving a random sample of older

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Key Points

This interprofessional deprescribing intervention successfully reduced inappropriate use of proton pump inhibitors among older adults.

More than 90% of participants in the intervention group reported being satisfied or very satisfied with the overall intervention, suggesting a high level of acceptance.

Further efforts to promote multiprofessional collaboration and conduct larger trials are needed to assess the impact of deprescribing on important clinical outcomes and patient-reported experiences.

adults attending primary care centres, found that PPIs were the most frequently prescribed class of inappropriate medications, accounting for approximately 45% of the sample [8]. Given the high prevalence of PPI use, the associated safety concerns and the significant financial burden that these medications impose on society, particularly given the demographic shifts associated with an aging population, it is essential to develop strategies to improve medication use quality and safety among older adults.

Deprescribing is a health professional-supervised intervention aimed at reducing or discontinuing medications that may cause harm or no longer provide benefit. The goal is to reduce the medication burden while improving patient outcomes [9–11]. Evidence suggests that deprescribing can improve clinical outcomes [12] and is more effective when it involves educational interventions and collaboration between patients, pharmacists and prescribers [13–16]. However, results for PPIs are not consistent [17], and the success of deprescribing interventions remains inconclusive, varying on factors such as intervention type, class of medicines and targeted population [18, 19].

Given the existing evidence and the fact that most prescribing occurs in primary care settings in Portugal, we developed a patient-centred, multidisciplinary deprescribing approach for PPIs in primary care. The Collaborative DepreScribing IntervENtion of PPIs on community-dwelling oldeR adults (C-SENIoR) pragmatic non-randomised controlled trial aimed to evaluate the effectiveness of a collaborative intervention involving community pharmacists and general practitioners in deprescribing inappropriate PPIs among community-dwelling older adults.

2 Methods

The C-SENIoR trial was a pragmatic, multicentre, non-randomised two-arm controlled trial with 6-month follow-up in Portuguese primary care, involving community pharmacies and family health units (FHUs) to deprescribe PPIs in mainland Portugal. A random design was not feasible because the intervention was developed on the basis of the interest expressed by two FHUs in participating with pharmacies in the trial.

The study protocol has been previously published [20]. The Ethics Research Committee of Nova Medical School, NOVA University of Lisbon and the Ethics Committee from the Local Health Unit Alto Minho, Portugal approved the study. .

2.1 Pharmacies, Family Health Units and Participants

Two intervention FHUs in two distinct municipalities were initially identified and recruited through a partnership with the Portuguese National Association of Pharmacies. A total of nine eligible intervention pharmacies were identified on the basis of the FHUs' geographic location. These pharmacies needed to serve patients from the FHUs and use the Sifarma® dispensing software to enable data extraction. Owing to this small number of pharmacies and FHUs in these areas, which limited the feasibility of randomisation, a prospective geographic location-based matching method was employed to identify control municipalities while minimising contamination. First, three-dimensional normalised Euclidean distance—based on per capita purchasing power, aging ratio and illiteracy rate [21]—was calculated for each municipality in Mainland Portugal, using the two intervention municipalities as separate reference points. Potential best-match control municipalities were then ranked in ascending order from smallest to highest distance.

Second, within these best-matched municipalities, potential control FHUs were identified by first matching their contractual type with the National Health Service (type A or B, which differ essentially in financing models) and then aligning their PPI prescription rate, measured in defined daily doses per 1000 inhabitants per day [22] for the registered older adults, with that of the intervention FHUs, allowing a 20% variation. The matching process aimed to identify regions where patients had characteristics similar to those in the intervention group (IG) and received comparable care through primary healthcare services. A larger pool of municipalities and potential control pharmacies was considered to balance the number of recruitment sites and patients across both trial arms, accounting for anticipated lower pharmacy adherence and patient recruitment in the control arm, as previously observed in similar studies [23]. A total of 11 control municipalities, comprising 17 matched FHUs and 61 pharmacies, identified using the same criteria as the intervention pharmacies, were considered eligible. Figure 1 illustrates the FHUs, pharmacies and patient inclusion through the trial.

Of the nine community pharmacies invited in the two intervention municipalities, eight (88.9%) agreed to participate. In the 11 control municipalities, 17 of 61 pharmacies (27.9%) accepted. Following training, 21 pharmacies were included in the study: 8 in the IG (2 municipalities) and 13 in the control group (CG) (10 municipalities), with patients from 2 and 16 FHUs, respectively.

Eligible participants were community-dwelling older adults (≥ 65 years), registered at the selected FHUs, with access to a telephone and using any PPI medication such as esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole (ATC/WHO A02BC) for more than 8 weeks (beyond which continued use is often unnecessary and associated with increased risk of adverse effects) [2, 3]. Exclusion criteria for patients were residing in nursing homes or assisted-living facilities, unable to communicate or speak in Portuguese, having cognitive impairments, or any other condition that hinders their understanding of the study objectives or the questionnaires as assessed by the community pharmacist (CP) who performed the recruitment. In both intervention and control pharmacies, the dispensing software generated an electronic pop-up window whenever a PPI was dispensed to remind CPs to systematically assess patients' eligibility.

A total of 166 patients enrolled in the study (87 in the IG and 79 in the CG), and 30 declined to participate (5 in the IG and 25 in the CG). The age distribution of those who refused (65–74 years: 53.6%, ≥ 75 years: 46.4%) and the proportion of females (57.7%) were similar to those of the participants ($p > 0.05$). The main reasons for refusal were unfamiliarity with this type of study ($n = 16$, 59.3%), lack of time ($n = 4$, 14.8%) and discomfort with sharing personal data ($n = 4$, 14.8%).

Of the enrolled patients, 159 (95.8%) completed the trial (84 (96.5%) in the IG and 75 (94.9%) in the CG) (Fig. 1).

Patient recruitment began on 28 April 2023 and ended on 15 November 2023 (latest data of follow-up, June 2024). Medical doctors, CPs and patients received no financial incentives for participating in the trial.

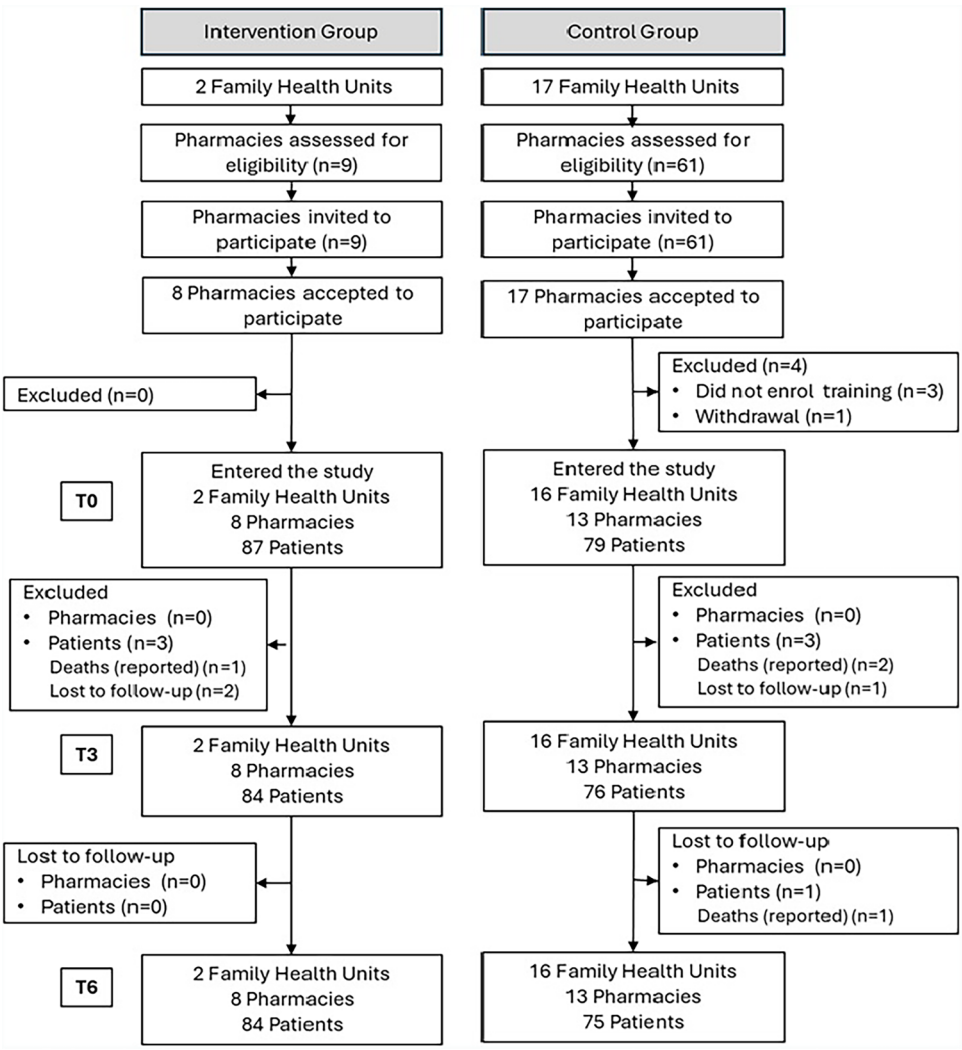

Fig. 1 Flowchart of community pharmacies, family health units and patients through the study

2.2 Intervention and Control

The multifaceted intervention involved a collaborative care pathway between CPs and general practitioners (GPs) to deprescribe inappropriate PPIs. Briefly, this patient-centred intervention comprised three main components. First, CPs recruited patients on the basis of PPI use duration (>8 weeks). Next, they assessed the potential inappropriate use of PPIs, considering the patient's self-reported clinical indication and provided both oral and written educational information using a patient information booklet developed explicitly for this study (Supplementary file 1). Additionally, a long-term medication list was elaborated, highlighting any moderate and severe drug–drug interactions (DDIs), and shared with the GP. Second, GPs, using the information provided by the CPs and the patient's medical records, evaluated the need for PPIs, addressed any other safety concerns and contacted the patient (preferably by telephone) to discuss the appropriateness of continuing PPIs or the strategy for deprescribing, if applied.

A national guideline for acid suppression therapy management with PPIs and their therapeutic alternatives was used in this trial as the deprescribing framework [2]. When appropriate, a tapering strategy was designated as the preferred approach to discontinue a PPI, although the final decision was left to GP discretion. Third, following the GP consultation, the CP was informed of the deprescribing decision (i.e. whether to maintain PPI as used or to initiate deprescribing, which could include stopping or reducing doses). CPs then conducted telephone follow-ups with participants to monitor the withdrawal process, when applicable. The intervention summary is displayed in Fig. 2.

Communication between CPs and GPs was facilitated through a paper-based 'Patient's Passport', where intervention-related data were recorded. A clinical research associate coordinated the exchange of this document between professionals. All participating CPs (intervention and control) attended a face-to-face training session provided by the research team. For the IG, the training included information on PPI therapeutics, along with detailed guidance on the study intervention and related procedures. Study materials were sent to the pharmacies via express mail prior to the training sessions.

Additionally, before the study began, pharmacists and GPs in the IG participated in an in-person meeting to review the patient eligibility criteria, intervention materials and study procedures. This included the national guideline for acid suppression therapy [2]. Further details of the intervention are available in the study protocol [20].

The comparator was usual care, i.e. patients received standard practice without any educational material or specific collaborative intervention.

2.3 Outcomes

Outcome data were collected at baseline, 3 months (± 1 month) and 6 months (± 1 month) follow-up. The primary outcome was successful deprescribing, defined as discontinuation or dose reduction of any PPI at 3 and 6 months post-enrolment, assessed at the patient level. PPI use or discontinuation was determined through patient self-reports during follow-up telephone interviews and pharmacy medication sales data. Patients were classified as either successfully deprescribed or not. Sales data were used to validate patients' reports on deprescribing, and all reports were confirmed.

The medical recommendation regarding PPI deprescribing (yes or no) and the self-reported withdrawal symptoms were also assessed.

Secondary outcomes included the effect of the intervention on several patient-reported outcomes (PROs) and drug-specific outcomes. PROs included patients' beliefs

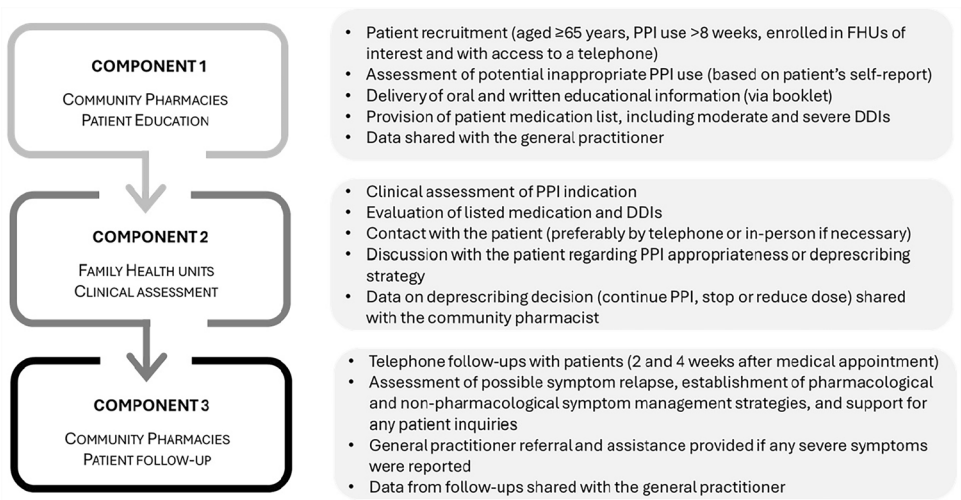

Fig. 2 Summary of C-SENIoR intervention procedures. DDIs, drug-drug interactions; FHUs, family health units; PPI, proton pump inhibitor

about PPIs, medication adherence, health-related quality of life (HRQoL) and the self-reported number of adverse drug events (ADEs) experienced, precisely the number and proportion of patients reporting at least one ADE (adverse event or undesirable effect that may be attributed to the use of any of the medications) in the previous 6 months.

Adherence was measured by the Measure Treatment Adherence (MTA) [24] questionnaire consisting of a seven-item, six-point Likert scale tool ranging from the anchor point 1 (always) to the anchor point 6 (never), with 'always' representing the lowest adherence point. Mean scores greater than or equal to 5 are considered adherent, corresponding to the responses 'rarely' or 'never' [24]. Patient beliefs about PPIs were measured by the Beliefs about Medicines Questionnaire (BMQ-specific) [25], an 11-item questionnaire with two subscales: Necessity (5 items) and Concerns (6 items). Items are rated on a five-point Likert scale (from 1 = strongly disagree to 5 = strongly agree), with subscale scores ranging from 5 to 25 (Necessity) and 6 to 30 (Concerns). A higher necessity—concerns differential score indicates higher perceived necessity and/or lower concerns [25].

HRQoL was assessed using the EQ-5D-5L generic instrument, which covers five health dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with five levels of functioning (from 1 = no problems to 5 = severe problems) [26]. Mean scores were calculated based on the EQ-5D-5L Portuguese tariffs [27].

Drug-specific outcomes included the number of long-term medications, the proportion of patients on polypharmacy (≥ 5 medicines) [28], those highly medicated (≥ 10 medicines) and identified moderate and severe DDIs were measured using the pharmacy medication dispensing data validated by patients' reports.

Satisfaction with the collaborative intervention was assessed exclusively in intervention group using a five-level Likert scale (from 1 = not at all satisfied to 5 = very satisfied). Data were collected via telephone interviews.

Additionally, to assess the fidelity of the intervention, process outcomes were considered, including the number and proportion of patients who had a medical appointment, the type of appointment (in-person or telephone), the time elapsed until the medical appointment and the number of pharmacist follow-ups.

2.4 Sample Size

Our hypothesis is that this intervention would achieve a minimum 20% absolute difference in the proportion of patients who discontinued or reduced their PPI dosage in the IG compared with the CG at 6-month follow-up, similar to results observed in previous studies involving patient education and collaboration between CPs and GPs [13, 29]. We considered that approximately 10% of the users who do not receive the intervention may naturally discontinue PPIs. Assuming a statistical significance of 5% and 90% power, for an allocation ratio of 1:1, the minimum total sample size to detect differences between IG and CG was estimated to be 178 patients (89 patients per group). Accounting for potential losses to follow-up of 20% of the patients, a total of 222 participants (111 per group) would be needed [20].

2.5 Statistical Analysis

Comparisons between patients who agreed to participate in the study and those who refused were performed using the chi-squared or Fisher's exact test for categorical variables. Comparisons comprised age class and sex. Reasons for refusal were described.

Baseline characteristics were described for all study patients and stratified by group. The IG and CG were compared using the Chi-squared or Fisher exact test for categorical variables and/or *t* test/analysis of variance (ANOVA) or nonparametric Wilcoxon/Kruskal–Wallis test for continuous variables.

Analysis were performed according to intention-to-treat. The primary outcome (discontinuation or dose reduction) analysis was performed using a generalised linear model (GLM) for binary outcome with an identity link function to estimate the absolute risk difference between the IG and CG in the proportion of patients who discontinued or decreased PPIs use at 3- and 6-month follow-ups, adjusted for age class, sex, body mass index, education level and self-rated health status. The relative risk and the number needed to treat (NNT) are also presented with their 95% confidence interval (CI).

To explore how characteristics such as sex, education level, body fat, self-rated health, PPI treatment duration and baseline medication burden (polypharmacy) influenced the effectiveness of the intervention, a subgroup analysis was performed to estimate the risk differences in deprescribing among patients in the intervention group with a medical indication for PPI deprescribing.

Secondary outcomes were computed using difference-in-differences (DiD) estimators to compare groups concerning changes from baseline to 6 months, in BMQ score, adherence MTA, HRQoL and long-term medication, polypharmacy, ADEs, patients with DDI and the number of DDI. GLM models were adjusted for age class, sex, body mass index (BMI), education level and self-rated health status. Analysis only considered patients for which outcome measures were available at follow-up (3 or 6 months).

Satisfaction with the intervention for those who successfully deprescribed PPIs versus those who did not was

compared using the Fisher exact test. Analyses were performed using 95% confidence intervals, and two-sided p-values < 0.05 were considered significant. SAS Enterprise Guide 7.15 (Cary, NC) software was used.

3 Results

3.1 Baseline Characteristics

No statistically significant differences were observed between IG and CG patients, as summarised in Table 1. They had a mean age of 74.2 years (SD 6.0 years), with 59.0% being female. Most patients (62.1%) had a maximum primary education (up to 4th grade), and 70.6% lived with a companion. On average, they had been taking PPIs for 10.6 years (SD 7.3 years), had 5.1 (SD 2.1) comorbidities and 81.9% were taking five or more medications. Additionally, about three-quarters (73.4%) were overweight or obese, and 56.4% reported a fair health state. GPs were identified as the initial prescribers of PPIs for the majority of patients (71.8%). The most commonly prescribed PPI was pantoprazole (40.4%), followed by omeprazole (26.5%), as detailed in Table 1. Among patients taking pantoprazole, approximately 71% were on a low dose of 20 mg per day, which is half the defined daily dose (DDD), as established by the ATC/WHO classification [22]. For omeprazole, about 93% of patients were taking the substance DDD of 40 mg per day.

The most frequently self-reported reasons for PPI use included gastric protection (26.5%), gastro-oesophageal reflux disease (21.1%), gastritis or dyspepsia (17.5%), and oesophagitis (16.9%).

3.2 Primary Outcomes

At the 3-month follow-up, 50.0% of patients in the IG successfully deprescribed PPIs, compared with 5.3% in the CG. The adjusted absolute risk difference in deprescribing among groups was 46.3% (95% CI 32.8–59.9%), with a NNT of 2.2. The relative risk of deprescribing PPIs among patients who received the intervention compared with those who did not was 9.6 (95% CI 3.6–25.6). At 6-month follow-up, the effect of the intervention remained similar, as detailed in Table 2. In most cases, deprescribing occurred within the first 3 months after the recruitment.

3.2.1 Subgroup Analysis for the Intervention Group

Among the 86 patients who attended the medical appointment, 60 (69.8%) received a recommendation to withdraw or reduce their PPI dosage. At the 6-month follow-up, 41 participants had successfully deprescribed. During the 4-week pharmacist follow-up, 52 patients were successfully monitored, of whom 55.8% reported no withdrawal symptoms. Among those who did experience symptoms, the most frequent were heartburn (36.5%) and epigastric pain (15.4%). Overall, 12 out of the 16 patients (75.0%) who did not successfully deprescribe had reported withdrawal symptoms, compared with 11 out of 36 (30.6%) who successfully deprescribed.

No significant interactions were observed between successful deprescribing and patient sex, age, educational level, self-reported health, body fat or other medication characteristics among the subgroup of patients in the IG with a medical indication to deprescribe. Absolute risk differences in deprescribing at 6-month follow-up by patient subgroup are summarised in Supplementary Table S1.

3.3 Secondary Outcomes

At trial completion, no significant differences ($p > 0.05$) were observed between the IG and CG in both PROs and drug-specific outcomes (Table 3). However, in relation to beliefs about PPIs, a significant difference in the Necessity–Concerns differential score was observed at baseline ($p < 0.001$), with the IG exhibiting lower necessity or higher concerns. Nevertheless, at 3-month follow-up, the score increased in the IG and decreased in the CG, with no significant difference between groups (adjusted difference = − 1.59; 95% CI − 1.35 to 4.53, $p = 0.290$).

Detailed results for the secondary outcomes are presented in Table 3.

3.3.1 Intervention Group Patient-Reported Experiences

Regarding satisfaction with the collaborative intervention, at the 6-month follow-up, most respondents reported being satisfied or very satisfied with the CPs and GP interventions, as well as with the overall experience (> 90%). No statistical differences ($p > 0.05$) were observed in the level of satisfaction between those who deprescribed and those who did not. Supplementary Fig. S1 in illustrates the satisfaction outcomes reported by IG participants.

3.4 Process Outcomes

Of the 87 patients in the IG, 86 (98.8%) attended a medical consultation with their GP, while 1 patient died before the consultation occurred. Most consultations were conducted via telephone (80.2%), with 16.3% held in person. The consultation type was unspecified for the remaining 3.5%. The average time between the pharmacist-led baseline intervention and the medical appointment was 50.2 days (SD 45.4

Table 1 Baseline patient characteristics

	All (n =166)	Intervention group (n = 87)	Control group (n = 79)	p Value for difference[1]
Sex, n (%)				
Female	98 (59.0)	51 (58.6)	47 (59.5)	0.909
Age, years				
Mean (SD)	74.2 (6.0)	74.4 (6.1)	74.1 (5.9)	0.897
Highest education level, n (%)				
No schooling or primary only (4th year)	100 (62.1)	57 (67.1)	43 (56.6)	0.330
Primary (6th or 9th year)	39 (24.2)	19 (22.3)	20 (26.3)	
Complete secondary (12th year) or college/university	22 (13.7)	9 (10.6)	13 (17.1)	
NR	5	2	3	
Household dimension, n (%)				
Alone	47 (29.4)	29 (34.9)	18 (23.4)	0.109
≥ 2 person	113 (70.6)	54 (65.1)	59 (76.6)	
NR	6	4	2	
Household monthly net income, EUR				
Mean (SD)	972.1 (777.0)	869.5 (674.0)	1088.5 (871.5)	0.054
NR	55	28	27	
Self-reported health, n (%)[2]				
Very poor	2 (1.2)	2 (2.3)	0	0.514
Poor	19 (11.7)	9 (10.3)	10 (13.2)	
Fair	92 (56.4)	47 (54.0)	45 (59.2)	
Good	48 (29.5)	27 (31.0)	21 (27.6)	
Very good	2 (1.2)	2 (2.3)	0	
NR	3	0	3	
Smoking status, n (%)				
Non-smoker	116 (71.2)	65 (75.6)	51 (66.2)	0.096
Ex-smoker	40 (24.5)	20 (23.3)	20 (26.0)	
Current smoker (yes)	7 (4.3)	1 (1.2)	6 (7.8)	
NR	3	1	2	
BMI (kg/m^2)				
Mean (SD)	28.0 (4.5)	27.8 (3.7)	28.2 (5.1)	0.808
Underweight/normal weight: < 25	41 (26.6)	21 (27.3)	20 (25.9)	0.884
Overweight: ≥ 25 and < 30	67 (43.5)	32 (41.6)	35 (45.5)	
Obesity: ≥ 30	46 (29.9)	24 (31.1)	22 (28.6)	
NR	12	10	2	
PPI substance, n (%)				
Pantoprazole	67 (40.4)	32 (36.8)	35 (44.3)	0.451
Omeprazole	44 (26.5)	28 (32.2)	16 (20.2)	
Esomeprazole	35 (21.1)	16 (18.4)	19 (24.1)	
Lansoprazole	17 (10.2)	9 (10.3)	8 (10.1)	
Rabeprazole	3 (1.8)	2 (2.3)	1 (1.3)	
Duration of PPI use, years				
Median (Q1–Q3)	10 (5–15)	10 (5–15)	10 (4–15)	0.679
Patients on ≥ 10 years	95 (57.0)	52 (59.8)	43 (55.8)	0.611
NR	2	0	2	
PPI initial prescriber				
General practitioner	115 (71.9)	62 (75.6)	53 (68.0)	0.465
Gastroenterologist	27 (16.9)	13 (15.9)	14 (17.9)	
Other	18 (11.2)	7 (8.5)	11 (14.1)	

Table 1 (continued)

	All (n =166)	Intervention group (n = 87)	Control group (n = 79)	p Value for difference[1]
NR	6	5	1	
Medication reimbursement scheme				
Pensioners	68 (41.0)	35 (40.2)	33 (41.8)	0.840
General/other	98 (59.0)	52 (59.8)	46 (58.2)	
Comorbidities[3]				
Median (Q1–Q3)	5 (4–6)	5 (4–6)	5 (4–6.5)	0.792
Top comorbidities				
Hypertension (NR = 6)	129 (80.6)	65 (76.5)	64 (85.3)	0.157
Hypercholesteraemia (NR = 7)	115 (72.3)	65 (76.5)	50 (67.6)	0.211
Arthritis (NR = 11)	82 (52.9)	47 (58.0)	35 (47.3)	0.181
Cataracts (NR = 11)	79 (51.0)	40 (47.6)	39 (54.9)	0.364
Anxiety (NR = 9)	57 (36.3)	30 (35.3)	27 (37.5)	0.775
Diabetes (NR = 5)	57 (35.4)	29 (33.7)	28 (37.3)	0.633

(1) Wilcoxon–Mann–Whitney/Chi-squared tests and Fisher's exact test; (2) health status was determined using the self-perceived health questionnaire (SRH)[30]; (3) based on a predefined list of the most common comorbidities in older adults. The option 'other' was also available

BMI, body mass index; NR, no response; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 2 Intention-to-treat analysis of primary outcome

Follow-up	No. who successfully deprescribed/no. of patients (%)		Adjusted absolute risk difference, % (95% CI)	No. needed to treat to discontinue PPI in one patient	Adjusted relative risk (95% CI)
	Intervention group	Control group			
3 months	42/84 (50.0%)	4/76 (5.3%)	46.3 (32.8–59.9)	2.2	9.6 (3.6–25.6)
6 months	41[a]/84 (48.8%)	4[b]/75 (5.3%)	44.3 (30.8–57.8)	2.3	8.9 (3.3–23.6)

Adjusted for age class (65–74 years, ≥ 75 years); sex (F, M); body mass index (< 25, 25–30, ≥ 30 kg/m^2); education level (≤ 4th grade, > 4th grade) and self-rated health status (very poor to fair, good to excellent)

[a]21 out of 41 (51.2%) completely discontinued the medication

[b]2 out of 4 (50.0%) completely discontinued the medication

days), ranging from a minimum of 7 days to a maximum of 178 days. On average, each patient received 1.5 follow-up contacts from the CPs (SD 0.68). For 69.0% (58 out of 84) of patients, the CPs completed all scheduled follow-ups: two for those with a deprescribing indication and one for those without a medical recommendation to deprescribe.

4 Discussion

4.1 Main Findings

The C-SENIoR intervention was effective in reducing PPI use at 3- and 6-month follow-ups compared with usual care. Among the patients who received the collaborative, patient-centred intervention, 48.8% had their PPI stopped or reduced, compared with 5.3% in the CG at 6 months, with a number needed to treat of 2.3. These findings align with previous studies aimed at reducing inappropriate PPI use. Clyne et al. evaluated a multifaceted intervention involving a pharmacist-led academic detailing with GPs to review medications with patients, supported by web-based algorithms and tailored patient information leaflets [29]. At the intervention completion, participants had significantly lower odds of having a prescription for PPIs at maximal dose compared with the CG (adjusted OR 0.30; 95% CI 0.14–0.68, p = 0.04), with a sustained reduction at 1-year follow-up (adjusted OR = 0.40, 95% CI 0.17–0.94, p = 0.04) [31]. Wong et al. examined the effect of a pharmacist deprescribing recommendations for GPs based on patients' questionnaires. Inappropriate PPI use significantly decreased from 79.9 to 30.4% in the IG, with no change in the CG (from 79.9 to 77.1%) [32]. Taken together, these trials suggest that collaborative deprescribing interventions involving CPs, GPs and patients in primary care settings effectively reduce inappropriate PPI use.

Table 3 Intention-to-treat analysis of secondary outcomes**:** patient-reported outcomes and drug-specific outcomes

	Intervention group	Control group	Difference-in-difference (95% CI)[a]	*p* Value
Patient-reported outcomes				
BMQ-Specific score: Necessity–Concern differential[1]				
Mean (SD)				
Baseline ($n = 81$ IG; $n = 79$ CG)	0.5 (6.0)	5.6 (5.9)		
3-month follow-up ($n = 56$ IG; $n = 46$ CG)	2.4 (5.1)	4.2 (5.2)		
Change at 3 months[b] ($n = 51$ IG; $n = 46$ CG)	1.14 (7.64)	− 1.54 (6.48)	1.59 (− 1.35 to 4.53)	0.290
Adherence (MTA score)[2]				
Mean (SD)				
Baseline ($n = 86$ IG; $n = 75$ CG)	5.7 (0.4)	5.8 (0.3)		
6-month follow-up ($n = 77$ IG; $n = 66$ CG)	5.8 (0.3)	5.8 (0.2)		
Change at 6 months ($n = 76$ IG; $n = 63$ CG)	0.09 (0.38)	0.05 (0.34)	0.04 (− 0.08 to 0.17)	0.507
Health-related quality of life[b] (HRQoL)[3]				
Mean (SD)				
Baseline ($n = 86$ IG; $n = 76$ CG)	0.81 (0.21)	0.84 (0.20)		
6-month follow-up ($n = 81$ IG; $n = 66$ CG)	0.82 (0.19)	0.84 (0.16)		
Change at 6 months ($n = 80$ IG; $n = 64$ CG)	0.01 (0.18)	− 0.01 (0.18)	0.04 (− 0.03 to 0.10)	0.238
Adverse drug events (ADEs)				
Patients with ADEs (*n*, %)				
Baseline ($n = 86$ IG; $n = 73$ CG)	9 (10.5)	4 (5.5)		
6-month follow-up ($n = 77$ IG; $n = 67$ CG)	7 (9.1)	9 (13.4)		
Change at 6 months[b] (%, SD) ($n = 77$ IG; $n = 62$ CG)	0.00 (4.63)	6.45 (5.28)	− 6.78 (− 20.38 to 6.82)	0.329
Drug-specific outcomes				
Long-term medications per patient				
Mean (SD)				
Baseline ($n = 87$ IG; $n = 77$ CG)	6.8 (2.7)	7.6 (3.2)		
6-month follow-up ($n = 84$ IG; $n = 73$ CG)	6.3 (2.6)	7.4 (3.3)		
Change at 6 months[b] ($n = 84$ IG; $n = 73$ CG)	− 0.48 (1.11)	− 0.19 (1.23)	− 0.24 (− 0.63 to 0.16)	0.238
Patients on polypharmacy (*n*, %)				
Polypharmacy (≥5)				
Baseline ($n = 87$ IG; $n = 77$ CG)	69 (79.3)	67 (87.0)		
6-month follow-up ($n = 84$ IG; $n = 73$ CG)	63 (75.0)	59 (80.8)		
Change at 6 months[b] (%, SD) ($n = 84$ IG; $n = 73$ CG)	− 4.8 (6.45)	− 5.5 (6.12)	1.80 (− 9.03 to 12.64)	0.744
Polypharmacy (≥10)				
Baseline ($n = 87$ IG; $n = 77$ CG)	15 (17.2)	18 (23.4)		
6-month follow-up ($n = 84$ IG; $n = 73$ CG)	10 (11.9)	17 (23.3)		
Change at 6 months[b] (%, SD) ($n = 84$ IG; $n = 73$ CG)	− 6.0 (5.47)	1.4 (6.92)	− 8.44 (− 18.88 to 2.01)	0.113
Drug–drug interactions[c] (DDIs)				
Mean (SD)				
Baseline ($n = 87$ IG; $n = 77$ CG)	0.87 (1.37)	1.25 (1.66)		
6-month follow-up ($n = 84$ IG; $n = 73$ CG)	0.89 (1.46)	1.19 (1.76)		
Change at 6 months[b] ($n = 84$ IG; $n = 73$ CG)	0.01 (0.59)	− 0.05 (0.76)	0.03 (− 0.19 to 0.25)	0.794
Patients with moderate DDIs (n, %)				
Baseline ($n = 87$ IG; $n = 77$ CG)	36 (41.4)	43 (55.8)		
6-month follow-up ($n = 84$ IG; $n = 73$ CG)	36 (42.9)	40 (54.8)		
Change at 6 months[b] (%, SD) ($n = 84$ IG; $n = 73$ CG)	1.2 (7.62)	− 1.4 (8.23)	4.37 (− 7.94 to 16.69)	0.486

CI, confidence interval; CG, control group; DDI, drug–drug interactions; IG, intervention group; SD, standard deviation

[a]Difference-in-difference analysis, adjusted for age class (65–74 years, ≥ 75 years); sex (F, M); body mass index (< 25, 25–30, ≥ 30 kg/m^2); education level (≤ 4th grade, > 4th grade) and self-rated health status (very poor to fair, good to very good)

[b]Follow-up measure minus baseline measure for paired sample

[c]Only moderate DDIs were identified on the bas sif patients' long-term medication lists, using the pharmacy safety software. The platform

Table 3 (continued)

integrates data from summaries of product characteristics, Stockley's Drug Interactions and Lexicomp. DDIs are classified as: (a) moderate if requiring monitoring, dose adjustment, or other management or (b) severe if potentially life-threatening, requiring medical intervention, or contraindicated for concurrent use

[1]BMQ-Specific, Beliefs about Medicine Questionnaire specific. Necessity ranges from 5 to 25, and Concerns from 6 to 30. Higher Necessity–Concerns differential score indicates higher perceived necessity and/or lower concerns [25]

[2]MTA, seven-item Measure Treatment Adherence. Mean score ≥ 5 is considered adherent [24]

[3]HRQoL estimated based on the EQ-5D-5L questionnaire and national tariffs [27]

The intervention might have been more effective if it had targeted only patients without a clinical indication for long-term PPI use, as defined in national guidelines for acid suppression therapy [2]. Eligibility was based on PPI use exceeding 8 weeks, as pharmacists lacked access to clinical records. Consequently, approximately 30% of IG patients received a GP's indication to continue their current therapy, which may have limited the overall intervention's impact. In contrast, 70% were advised to stop or reduce their dosage, confirming the high prevalence of inappropriate PPI prescribing among community-dwelling older adults in Portugal [33, 34]. However, the rationale for each medical decision was not consistently or systematically documented, which limited the ability to describe the criteria guiding the decision to maintain or deprescribe the PPI.

Providing pharmacists access to electronic clinical records and implementing artificial intelligence for risk prediction and decision support could enable them to better identify candidates for community-based deprescribing service [7, 35]. This approach could enhance the effectiveness of the intervention, potentially reducing costs and the NNT. Additionally, future research should explore how different deprescribing methods, such as tapering, abrupt discontinuation, or other approaches, may influence deprescribing outcomes.

Moreover, the C-SENIoR intervention was designed with a patient-centred approach, emphasising the swift exchange of information between health professionals via paper records, expanding the CP's role as a patient educator and supporter during the deprescribing process. This approach aimed to address common barriers to deprescribing, such as lack of information, poor communication, fragmented care, limited time available for GPs, concerns about reputational damage and the fear that patients may perceive deprescribing as an 'abandonment of care', mainly when they are satisfied with their current medications and perceive them as necessary [36–38]. On a broader deprescribing scale, developing and implementing a technological communication channel among CPs, GPs and other healthcare professionals should be prioritised to enhance patient-centred care and facilitate intervention monitoring throughout the entire process. This approach would promote engagement and satisfaction among both healthcare professionals and patients [35, 37].

In this pragmatic trial, there were some deviations from the planned intervention. For some participants, the time between the community pharmacy-based educational intervention and the medical appointment exceeded the expected 2–3 weeks, extending to 178 days. Additionally, around 30% of patients did not complete all scheduled follow-ups owing to incomplete monitoring by pharmacists. These delays or missed follow-ups may have affected the intervention's acceptability by creating a perceived lack of continuity of care [38, 39]. Successfully implementing deprescribing services requires integrating these procedures into routine practice, possibly supported by performance-based financial incentives [39].

Despite these deviations, the intervention's effect on PPI deprescribing outcomes and patient satisfaction with the professionals' involvement was notably high. Although approximately 25% of responses were missing for specific satisfaction questions regarding the CP's or GP's intervention during the 6-month follow-up, most participants (74 out of 84) answered the overall satisfaction question. Among these, 35.1% reported being satisfied, and 59.5% were very satisfied, with no significant differences ($p > 0.05$) between participants who had their medications deprescribed and those who did not. In the interpretation of these results, we should not exclude the potential influence of the existing relationship of proximity and loyalty often established between patients and these professionals in Portugal [40].

This trial did not demonstrate evidence of an effect of the intervention on any of the assessed PROs or drug-specific outcomes. However, this does not necessarily imply that the intervention had no potential impact on the secondary outcomes [41]. Nevertheless, no statistically significant improvements were observed in the IG compared with the CG at follow-up, and any potential differences would be unlikely to be clinically relevant, even if statistical significance had been achieved. Several systematic reviews [12, 42–44] and overviews of systematic reviews [45] have investigated the effects of deprescribing interventions on PROs, medication burden and safety, often reporting insufficient, mixed or limited evidence of their impact. Moreover, this particularly study was not powered to detect differences in these outcomes, as a much larger sample size than that estimated for the primary outcome would likely be required owing to the small magnitude of the expected differences

between groups for these outcomes. Furthermore, a smaller-than-estimated sample size was achieved in this study. The reasons were multifaceted: older population's reluctance to receive phone calls for data collection owing to concerns about fraud, pharmacists' limited time to participate in the study, delays between recruitment and medical consultations caused by heavy workloads, several doctors' strikes during the study, and pharmacists' hesitation to recruit participants out of concern that patients would not receive timely clinical follow-up and might become demotivated, as reported during pharmacies trial monitoring.

Regarding self-reported ADEs, our findings suggest that the intervention did not increase the overall likelihood of reporting ADEs in the IG compared with the CG. However, within the IG, 44.2% of patients with a medical recommendation for deprescribing reported withdrawal symptoms when directly assessed by the pharmacist. At 6 months, 75.0% of those who did not successfully deprescribe had reported withdrawal symptoms, compared with 30.6% among those who deprescribed successfully. These results align with previous studies indicating that symptom recurrence is a common barrier to successful deprescribing [39], underscoring the importance of a patient-centred approach and close symptom monitoring to minimise its effects and support adherence to deprescribing efforts.

As for HRQoL, the absence of a measurable and statistically significant effect aligns with findings frequently reported in the literature [12, 42–45]. Possible reasons include the combination of specific targeted medication and population characteristics [42], or an insufficient follow-up time to capture all potential interventions' effects [29, 42]. Concerning adherence, although the C-SENIoR intervention incorporated key adherence-promoting elements, such as health education [46] and multi-disciplinary collaboration [47], no significant differences were observed between the IG and CG. This may be due to high baseline adherence, limited sensitivity of the measurement tool [46] or the fact that the intervention did not significantly reduce overall medication burden, a factor inversely associated with adherence. These findings are consistent with a systematic review conducted by Ulley at al. that found insufficient evidence to demonstrate a beneficial effect of these interventions on adherence [48].

For the patients' beliefs towards PPI, the differential between necessity and concern was used [25]. At baseline, participants in the IG exhibited greater concern or lower perceived necessity compared with the CG ($p < 0.001$). Although the questionnaire was administered before the educational intervention, the trial invitation briefly outlined its objectives, the risks of prolonged PPI use and intervention steps, which may have influenced patients' initial perceptions. However, at the 3-month follow-up, no significant differences were observed between groups. This may reflect a true absence of the intervention effect, as reported in other studies [29], or may reflect reporting bias, since some patients who had already discontinued PPI had doubts about the questions, skipping some items, preventing the use of the questionnaire in the analysis.

4.2 Strengths and Limitations

Strengths of this study include its being, to the best of our knowledge, one of the first collaborative studies between CPs and GPs, as well as the first controlled trial on deprescribing interventions conducted in Portugal. Additionally, we believe that the C-SENIoR trial will provide relevant evidence on the impact of medication withdrawal services in primary care for community-dwelling older adults—a setting less explored compared with hospitals, long-term care or residential facilities [49].

Its pragmatic design, allowing for some variability, enhances the external validity of the findings and provides valuable insights into the barriers and facilitators of implementing and accepting such services, particularly among older outpatient adults. Moreover, this study assessed different categories of PROs (clinical and drug-related) and experiences with the intervention, offering valuable insights into the patient-centred perspective—a crucial yet often unexplored aspect of deprescribing research [50]. Additionally, a patient leaflet was specifically designed and tested for this trial, considering the characteristics of the Portuguese population.

Furthermore, the intervention might have encouraged close collaboration between GPs and CPs, potentially benefitting other patients in different circumstances. This signifies a potential positive spillover effect of the intervention, which was not measured.

Several limitations of this study must be acknowledged. First, the study was conducted in only 12 municipalities of Mainland Portugal, with the intervention implemented in two of them, meaning the population may not represent the entire country. Importantly, no significant differences were observed in participant characteristics between the IG and CG. Moreover, to account for potential confounding, the outcome analysis was adjusted for baseline covariates. Second, as this was a quasi-experimental design, the intervention sites were pre-determined, and FHUs that had previously agreed to participate in the trial may have exhibited a higher interest in this area of research, potentially leading to greater engagement from their professionals and influencing the outcomes.

Third, we did not achieve the estimated sample size, which reduced the statistical power of the analysis. However, for the primary outcome, this was not relevant owing to the substantial effect of the intervention compared with the

CG. Future research should also consider adequately powering deprescribing studies to thoroughly examine outcomes beyond the effects on the targeted medications.

Fourth, it was not possible to assess time to PPI discontinuation using survival analysis owing to issues in reporting the start date of deprescribing, particularly in cases involving changes in posology, which could not be anticipated. However, it was observed that deprescribing occurred in most cases within 3 months after the start of the intervention.

4.3 Implications for Future Policy and Practice

Inappropriate PPI prescribing was common among older adults. The effectiveness of this study in reducing PPI use, if implemented on a national scale, could provide significant clinical and economic benefits for both patients and the healthcare system. Reducing PPI use directly correlates with lower medication costs for patients and the National Health Service, which is responsible for reimbursing these treatments [51]. Moreover, while this short-term study did not demonstrate improvements in PRO or overall medication burden, reducing PPI use may help mitigate the risk of occurrence of adverse events associated with long-term use, such as chronic kidney disease, dementia, fractures and pneumonia, thus avoiding potentially indirect healthcare costs [52, 53].

This study highlighted the importance of interprofessional collaboration in healthcare. The intervention included an initial pharmacist-led educational session that sparked a discussion on PPI and deprescribing, followed by a clinical assessment involving a telephone consultation with the patient to reach a mutually agreed decision on deprescribing, as well as pharmacist-led withdrawal monitoring, all supported by an exchange of information among health professionals. This approach proved effective in the short term while minimising strain on healthcare systems, ensuring patient understanding and maintaining follow-up. For larger-scale interventions, ensuring the availability of technological communication channels among healthcare professionals is essential. This can only be achieved through governmental policies that enhance systematic infrastructure support, secure adequate funding and promote integration into existing healthcare technological systems.

Given that collaborative efforts involving multidisciplinary teams, the use of clinical decision-making algorithms and patient involvement are effective strategies [49], governments should also promote public initiatives that enhance the development of deprescribing interventions, while health professionals must continue to pursue multidisciplinary collaborative approaches to support patients in successfully discontinuing inappropriate medications. In this context, healthcare system reforms should explore incorporating financial incentives to support professionals in delivering protocol-driven deprescribing interventions aligned with performance-based remuneration programs. Further research is needed to assess whether the benefits demonstrated in this trial justify the associated implementation costs.

5 Conclusions

To our knowledge, this is the first controlled trial conducted in Portugal to study the effectiveness of a collaborative, patient-centred deprescribing intervention on community-dwelling older adults taking long-term PPIs. The positive impact of this intervention on reducing inappropriate PPI use underscores the need for health professionals and researchers to continue developing, implementing and enhancing multidisciplinary collaborative services to support patients in safely discontinuing high-risk medications. Longer study periods are needed to thoroughly assess the long-term outcomes and sustainability of the deprescribing intervention. These efforts should be supported by governmental actions promoting education and multidisciplinary initiatives facilitated by electronic communication channels to ensure effective cooperation and a patient-centred approach. Additionally, policy initiatives and healthcare system reforms should consider implementing financial incentives to encourage professionals to provide protocol-driven deprescribing services to optimise medication use and reduce inappropriate prescriptions among older adults.

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Declarations

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Conflicts of interest disclosure Sónia Romano, António Teixeira Rodrigues, Isabel Guerreiro and José Guerreiro are researchers at CEFAR/

Infosaúde, the research centre of the ANF, which has interests in collaborative public health interventions and supported the research. Luis Monteiro is a GP and a researcher with an interest in older adults' studies. João Braga Simões is a researcher and was a GP in one of the interventions FHUs. Nuno Lunet and Julian Perelman are academics. The involvement of academic independent researchers, who do not receive any fees for collaboration, ensures that these interests do not influence the analysis and interpretations of the study results. The trial results included in this manuscript are the exclusive responsibility of the research team.

Availability of data and material The data generated and/or analysed in this study are available from the corresponding author on reasonable request.

Ethics approval This study was approved by the Ethics Research Committee of Nova Medical School, NOVA University of Lisbon and the Ethics Committee of the Local Health Unit Alto Minho, Portugal. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments, with the exception that this trial was retrospectively registered at ISRCTN registry (ISRCTN49637686). This occurred owing to multiple postponements of the study start date and site relocation. Registration was completed shortly after recruitment commenced.

Consent to participate Written informed consent was obtained prior to enrolment from all participants.

Consent for publication Not applicable.

Code availability Not applicable.

Authors contribution Sónia Romano: conceptualisation, formal analysis, methodology, investigation, supervision, project administration, writing—original draft. António Teixeira Rodrigues: conceptualisation, methodology, resources, writing—review and editing. José Guerreiro: formal analysis, methodology, writing—review and editing. João Braga Simões: investigation, supervision, writing—review and editing .Isabel Guerreiro: resources, investigation, writing—review and editing.Luis Monteiro: conceptualisation, methodology, writing—review and editing. Nuno Lunet: formal analysis, methodology, writing—review and editing. Julian Perelman: conceptualisation, methodology, investigation, writing—review and editing.

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