


Can pain be self-managed? Pain change in vulnerable participants to a health education programme

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Abstract

Chronic pain exerts a significant impact on the quality of life, giving rise to both physical and psycho-social vulnerabilities. It not only leads to direct costs associated with treatments, but also results in indirect costs due to the reduced productivity of affected individuals. Chronic conditions can be improved by reducing modifiable risk factors. Various educational programs, including the Chronic Disease Self-Management Programme (CDSMP), have demonstrated the advantages of enhancing patient empowerment and health literacy. Nevertheless, their efficacy in addressing pain symptoms has received limited

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attention, especially concerning vulnerable populations. This research aims to assess the effectiveness of the CDSMP in alleviating pain among socio-economically vulnerable participants with chronic conditions. By accounting for a wide range of variables, and using data from the EFFICHRONIC project (EU health programme), we investigated the changes in pain levels after the intervention, among 1070 participants from five European countries. Our analyses revealed a significant reduction in pain following the intervention. This finding supports the notion that training programs can effectively ameliorate pain and alleviate its impact on the quality of life, particularly in vulnerable populations. Younger participants, as well as those with higher education levels and individuals experiencing higher levels of pain at baseline, were more likely to experience a reduction in their pain levels. These findings underscore the importance of recognising the social determinants of health.

The study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=ISRCTN70517103) (ISRCTN70517103).

KEYWORDS

chronic pain, low income, patient education, quality of life, vulnerable populations

Highlights

- Chronic pain impacts one-fifth of the European population.
- Its prevalence is higher in people with lower incomes.
- Participants with vulnerabilities engaged in the Chronic Disease Self-Management Programme.
- Following the intervention, their pain levels significantly decreased.

1 | INTRODUCTION

Chronic conditions are one of the greatest challenges for healthcare systems worldwide, and may account for nearly 60% of overall mortality.¹ Their increasing prevalence has huge consequences for policy and healthcare.^{1,2} Several studies reported a higher risk of chronic condition in vulnerable populations.^{3,4} Socio-economic status indeed affects modifiable risk factors of chronic conditions,^{5–8} so that patients living in poverty are more likely to be in poor health and to have disabling conditions. Vulnerability may thus promote the incidence of chronic conditions, but it can also be the consequence of chronic condition, which aggravates social vulnerability and can

precipitate people into precarity through loss of work.^{9,10} Yet, patients with a low socio-economic status have poorer access to health care.^{11,12} During the COVID-19 pandemic, in particular, people from socio-economically deprived groups and minorities reported challenges in accessing pain relief, health care services, and psychological support.¹³

In several chronic conditions, pain is one of the main symptoms altering the patients' quality of life. It should therefore be an important objective of integrated care. Pain induces multiple repercussions on quality of life, sleep, mood, physical activity, self-perceived health, social relations, work, and income. Indeed, pain imposes a significant emotional and physical burden on those affected. It can therefore lead to physical, psychological and social vulnerabilities.¹³⁻¹⁵

Pain complaints cause a large proportion of physician visits.^{16,17} As an example, back pain is experienced by 80% of the US population at some time in their lives,¹⁸ and prevalence in the elderly is estimated to be as high as 49%.¹⁹ Consequently, pain puts an enormous economic burden to healthcare systems.^{20,21} Furthermore, pain-related conditions result in absenteeism, disability retirement, and retiring prematurely and therefore reduces the productivity and competitiveness of the working population.²²

The prevalence of chronic pain is 19% in Europe.²³ The aetiology of chronic pain is complex, and is influenced by a range of biochemical, psychosocial and behavioural factors.²⁴ There are indications that the prevalence of chronic pain is influenced by a variety of socioeconomic and sociodemographic factors, such as age, gender, educational attainment, and income.²⁵ Chronic pain is also tightly and reciprocally linked to psychological distress,²⁶ and influenced by health literacy.²⁷

Chronic conditions can be prevented or controlled by reducing modifiable risk factors.^{28,29} A growing number of health education programs have shown positive effects.^{30,31} Among them, the 'Chronic Disease Self-Management Programme' (CDSMP)³² has demonstrated its effectiveness in reducing key risk factors and visits to healthcare professionals.³³⁻⁴⁴

However, research has not extensively explored the impact of the CDSMP on pain, especially in vulnerable populations. The CDSMP is expected to achieve greater health gains in participants with a low socioeconomic status, because they have fewer opportunities to adhere to a healthy lifestyle, more adverse chronic conditions, and a poorer overall health.^{28,45} Vulnerable people therefore represent patients with the greatest need for education and support.

However, patients with a low socio-economic status are less likely to participate in such training programs.^{11,12} Barriers limiting the implementation of self-management have been identified in vulnerable populations, characterised by a lower self-efficacy and a weaker adherence to self-management programs.^{46,47} Moreover, vulnerable people differed in support preferences⁴⁸ and a better tailoring of self-management approaches are necessary to address their specific requirements.

Our study aimed to evaluate the effectiveness of the CDSMP in reducing pain intensity among vulnerable individuals with a chronic condition participating in the EFFICHRONIC programme.⁴⁹ We compared their answers to a questionnaire at baseline, and after participating to the programme. This study is the first evaluation of the CDSMP's effectiveness in improving pain symptoms within vulnerable populations. We have also identified the predictive factors for the effectiveness of the CDSMP, facilitating the recognition of target populations that may necessitate an adaptation of this programme.

2 | METHODS

2.1 | Study design

The research project EFFICHRONIC is a prospective study based on the CDSMP intervention, involving socio-economically vulnerable participants with a chronic condition. To enhance sample representativeness, the study

was designed as multicentric and conducted in five European regions (Occitanie in France, province of Genoa in Italy, principality of Asturias in Spain, region of Rotterdam in the Netherlands, and the region of London in the United Kingdom). The programme EFFICHRONIC is part of the Third EU Health Programme, aimed at addressing the chronic disease challenge.

Vulnerability refers to a wide range of groups, including the economically deprived, ethnic minorities, the elderly, or those who encounter barriers to accessing health care (geographical isolation, low access to public transportation, lack of social networks).⁵⁰

The CDSMP intervention^{41,51} has been developed 40 years ago, and has since been implemented in more than 20 countries. It relies on empowerment, and the development of health-related social and cognitive skills, that are useful to better manage symptoms, such as pain.²⁷ The underlying conceptual elements in CDSMP are the self-efficacy theory, confidence building, pair-to-pair education, recognition of the social determinants of health, and community participation. The principle is to work under a problem-solving framework to reach individual solutions by collaborative means. Strengthening the ability of each individual to make decisions and find the adequate way to acquire a healthier lifestyle—understood as a whole (motivation, proactive behaviour, nutrition and physical activity)—improves their quality of life. The intervention consists in a series of six workshops, 2.5 h each, which are held once a week, for 6 weeks. One health professional and one peer, both trained in the CDSMP principles, led the series of workshops, attended by about 15 participants.

Our study has a pre-post design: it is based on data from an auto-questionnaire including various validated scales, filled before the start of the intervention (baseline), and 6 months later (follow-up).

The study follows the directives of the Helsinki declaration and the corresponding ethical regulations are being respected at each study site. The protocol was approved by the French ethics committee (CPP SOOM I, study number 9788), by the Regional Ethics Committee of Liguria (study number 152-2018), by the Medical Ethics Review Committee of the Erasmus MC University Medical Center, Rotterdam (MEC-2017-1116), and by the Research ethics committee of the Principality of Asturias (study number 20/17). In the United Kingdom, the Health Research Authority was consulted and it was concluded that approval from an ethics committee was not necessary. Written consent was obtained from all participants.

2.1.1 | Sample

A total of 2951 participants have been recruited in 2019 across the five pilot sites to receive the CDSMP intervention.^{49,52} Inclusion criteria for the intervention were:

- Aged at least 18;
- At least one chronic condition (according to the International Classification of Primary Care-2), that has been present for at least 6 months (or being a caregiver of such a patient);
- At least one vulnerability criteria among the following: older people (over 65) living alone or in retirement homes, or in a situation of social or family isolation; persons receiving a disability pension or allowance; ethnic minorities; legal immigrants, refugees and asylum seekers (whose residence has been known for at least 6 months); or low income (defined as below the poverty line at 60% of the median standard of living for the year 2015⁵³).

In this study, only participants with at least one chronic condition have been included: the caregivers have been excluded. Among them, individuals without pain at baseline were further excluded (294 participants). Consequently, our analyses focused on participants with a chronic condition and non-null initial pain.

2.2 | Variables

Baseline and follow-up questionnaires included many self-reported items. The item on pain intensity from the instrument EQ-5D-5L⁵⁴ was our main outcome: pain was assessed on a 0–4 scale (0: *I have no pain or discomfort*; 1: *I have slight pain or discomfort*; 2: *I have moderate pain or discomfort*; 3: *I have severe pain or discomfort*; 4: *I have extreme pain or discomfort*). The instruments from which were extracted the variables used in the present study are summarised in Table 1. Sleep problems and fatigue had been assessed using 0–10 visual analog scales. The quality of life had been assessed by 0–100 continuous scores summarising its physical and mental components. Depression was treated as a binary variable, assigned a value of 1 when the depression score exceeded 10. Self-perceived health was based on a 100-level visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The baseline questionnaire additionally included socio-demographics: age, sex, education level with 3 categories (low: primary or lower, middle: secondary, high: tertiary or higher), household composition with 2 categories (living alone, or not).

2.3 | Data analysis

All data have been handled confidentially and scientific data was stored pseudo-anonymously. Statistical analyses have been performed using R version 4.0.3.⁶¹

Logistic regressions have been performed for investigating the factors associated with the probability of being lost to follow-up (dichotomous outcome variable). We then compared the intensity of pain before and after participating to the programme. Differences between baseline and follow-up measurements have first been assessed by means of a Mann–Whitney *U* test. Effect size was evaluated using Cohen's *D*. In order to identify the factors associated with pain change after participating to the programme, we used as the outcome the difference between baseline and follow-up, as recommended in such situations.⁶² Firstly, univariable models were used and secondly, a multivariable model was built using those variables that had a significant effect in univariable models ($p < 0.05$, p -values being corrected for multiple testing⁶³).

2.4 | Missing data

The average proportion of missing values across all variables of interest in the dataset at baseline was 4.3%. However, at follow-up, the variable 'pain intensity' had 33.9% missing values, the same variable at baseline having 0% missing. An evaluation of the missing data suggested that multiple imputation was advisable. Indeed, the analysis of complete cases only can introduce bias and lead to a substantial reduction of statistical power,⁶⁴ especially if it is plausible that the data are not completely missing at random. To handle missing data, we used a multiple imputation approach using the R package 'missRanger',⁶⁵ which combines random forest imputation with predictive mean matching. Prior to all analyses, we imputed 5 datasets, with a maximum of 10 iterations specified for each imputation. Each imputation was also weighted by the degree of missing data for each participant, such that the contribution of data from participants who had more missing information was weighted down in the imputation. We set the maximum number of trees for the random forest to 200 but left all other random forest hyperparameters at their default. Parameter estimates for all five datasets were pooled to provide more accurate estimates. A sensitivity analysis was also performed on the complete cases (without missing data imputation).

TABLE 1 The instruments used in this study.

Name of instrument	Description	Simplified variable	Number of items
EQ-5D-5L ⁵⁴	Mobility, self-care, activity, pain, anxiety		5
Euro-Qol visual analogue scale (EQ VAS) ⁵⁵ : experienced current general health	100-level visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'		1
Physical exercise (developed specifically for the CDSMP)	Time spent weekly on various activities such as walking, swimming, cycling, and aerobics	Dichotomous variable (0 if the score was below the median, 1 if the score was above)	6
International Physical Activity Questionnaire (IPAQ) ⁵⁶	Sedentary behaviour: week and week-ends' numbers of hours sitting daily	Standardised variable combining weeks and week-ends	2
Patient Health Questionnaire (PHQ-8) ⁵⁷	Depression scale	Dichotomous variable (0 if PHQ-8 <10, 1 if PHQ-8 ≥10)	8
Sleeping problems and fatigue (developed specifically for the CDSMP)	10-level visual analog scales		2
SF-12 ⁵⁸	Health-related quality of life	Two 0–100 continuous scores summarising the physical and mental components of the quality of life	12
Gijon's socio-familial evaluation scale ^{59,60} : income	(1) No income or less than minimum pension allowance, (2) minimum pension (social welfare or disability pension), (3) from the minimum pension to the minimum wage, (4) from the minimum wage to 1.5 times the minimum wage, (5) more than 1.5 times the minimum wage (income scales were adjusted to the local situation in each country)		1
Gijon's socio-familial evaluation scale ^{59,60} : social relationships	(1) Doesn't leave the house and doesn't receive visits, (2) doesn't leave the house but receives visits, (3) only relates to family or neighbours/friends, (4) relates to family <i>and</i> neighbours/friends, (5) has social relationships		1

3 | RESULTS

Data were analysed for a total of 1070 participants (Figure 1) in five countries (France 171, Italy 192, The Netherlands 175, Spain 277, The United Kingdom 255). Among them, 329 were men (31%) and 733 were women (69%). The sex ratio varied across countries, ranging from 50% of women in the UK to 80% in Italy. Average age was 60 years (± 15 s.d.). Range and mean values of the examined parameters are reported in Table 2.

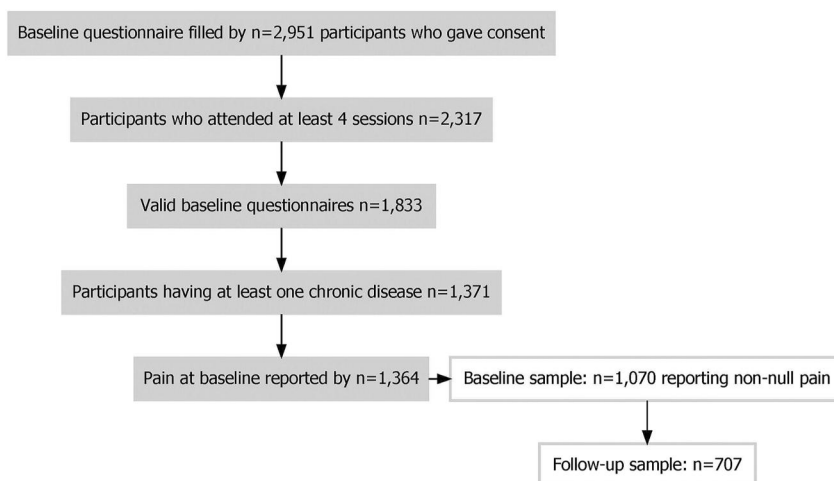


FIGURE 1 Flow chart of sample selection and attrition.

3.1 | Attrition: Are lost to follow-up participants different?

Among the 1070 individuals who reported a pain score higher than 0 at baseline, 363 had missing data for the pain variable at follow-up (33.9%), either because they were excluded (if they missed more than 2 workshops), or because they did not answer the follow-up questionnaire. This resulted in a complete cases sample of 707 participants.

Attrition rate did not differ between men and women (Chi-square test $p = 0.2$). Younger participants were more likely to be lost (median age category of lost participants: 8 i.e. 55–60 years, against 9 i.e. 60–65 years for followed participants, Wilcoxon rank test: $W = 139,350$, $p = 0.0008$). Follow-up was better in the UK (only 21% participants lost to follow-up) than in other countries, which did not significantly differ between them (between 36% and 40% lost). This is probably because, in the UK, the providers of the intervention were already well established and experienced in carrying such programs out.

Using a multivariable logistic regression, we found that, after adjustment, the variables that were significantly associated with the probability of being lost were: country ($p < 0.0001$), age (younger participants were more likely to be lost, $p = 0.0005$), and education (less educated participants were more likely to be lost, $p = 0.02$) (Supplementary Figure S1).

3.2 | Pain change: Comparison between baseline and follow-up pain

In complete cases ($N = 707$), the intensity of pain was on average lower at follow-up (1.51 ± 0.96 s.d.) than at baseline (1.83 ± 0.87 s.d.) (Figure 2A). This difference was significant (Wilcoxon rank test $W = 39,834$, $p < 10^{-15}$), but the effect size (Cohen's D) was 0.33, which is considered as a rather weak effect (it is usually considered that 0.2 is weak, 0.5 medium, and 0.8 strong).⁶⁶ Pain decreased on average in all countries (Figure 2B). Combining the five imputed datasets ($N = 1070$ in each dataset) showed a similar trend: at follow-up the average pain was lower (1.61 ± 0.95 s.d.) than at baseline (1.93 ± 0.90 s.d.). All Wilcoxon tests were significant (with p values ranging from 10^{-15} to 10^{-8}), with effect sizes (Cohen's D) ranging from 0.18 to 0.29.

TABLE 2 Description of the examined parameters.

Variable	Stats/values	Freqs	% Of valid	Missing
Country [factor]	1. FR	171	16.0%	0 (0.0%)
	2. IT	192	17.9%	
	3. NL	175	16.4%	
	4. SP	277	25.9%	
	5. UK	255	23.8%	
Sex [factor]	1. Men	329	31.0%	8 (0.7%)
	2. Women	733	69.0%	
Age category [integer]	Mean (s.d.): 8.8 (2.9) min < med < max: 1 < 9 < 15 IQR (CV): 4 (0.3)	15 distinct values		14 (1.3%)
Education level [factor]	1. Low	210	20.0%	19 (1.8%)
	2. Middle	667	63.5%	
	3. High	174	16.6%	
Income level [factor]	1. Very low	70	7.0%	63 (5.9%)
	2. Low	151	15.0%	
	3. Middle	193	19.2%	
	4. High	306	30.4%	
	5. Very high	287	28.5%	
Social relationships [factor]	1. Very low	32	3.2%	78 (7.3%)
	2. Low	26	2.6%	
	3. Middle	130	13.1%	
	4. High	489	49.3%	
	5. Very high	315	31.8%	
Household composition [factor]	1. Alone	348	33.1%	20 (1.9%)
	2. With others	702	66.9%	
Physical exercise [factor]	1. Less than median	613	57.8%	10 (0.9%)
	2. More than median	447	42.2%	
Sedentarity [numeric]	Mean (s.d.): 5.9 (3) min < med < max: 0 < 5.5 < 18 IQR (CV): 4 (0.5)	34 distinct values		129 (12.1%)
Fatigue [integer]	Mean (s.d.): 5.9 (2.7) min < med < max: 0 < 6 < 10 IQR (CV): 4 (0.5)	11 distinct values		18 (1.7%)
Sleep problems [integer]	Mean (s.d.): 5.2 (2.9) min < med < max: 0 < 6 < 10 IQR (CV): 4 (0.6)	11 distinct values		15 (1.4%)
Depression [factor]	1. No depression	620	63.3%	90 (8.4%)
	2. Depression	360	36.7%	

TABLE 2 (Continued)

Variable	Stats/values	Freqs	% Of valid	Missing
Physical QoL [numeric]	Mean (s.d.): 38 (10.7) min < med < max: 8.9 < 38.4 < 61.4 IQR (CV): 16.2 (0.3)	914 distinct values		126 (11.8%)
Mental QoL [numeric]	Mean (s.d.): 41.2 (10.2) min < med < max: 11.9 < 41.6 < 68.5 IQR (CV): 14.4 (0.2)	914 distinct values		126 (11.8%)
Self-perceived health [integer]	Mean (s.d.): 58.6 (20.7) min < med < max: 0 < 60 < 100 IQR (CV): 30 (0.4)	62 distinct values		21 (2.0%)
Pain intensity at baseline [factor]	1: Low	469	43.8%	0 (0.0%)
	2: Rather low	361	33.7%	
	3: Rather high	196	18.3%	
	4: High	44	4.1%	
Pain intensity at follow-up [factor]	0: No pain	102	14.4%	363 (33.9%)
	1: Low	275	38.9%	
	2: Rather low	209	29.6%	
	3: Rather high	108	15.3%	
	4: High	13	1.8%	

3.3 | Factors influencing the amplitude of pain change

In raw data, the change in pain depended on initial pain: pain decreased more when it was greater at baseline (Figure 2C). Because this may in part reflect a regression to the mean effect,⁶⁷ in the following multivariable analyses of the change in pain, the effect of initial pain was controlled for.

Univariable linear models on the imputed data ($N = 1070$) showed that country, age, education, and pain at baseline were significantly associated with pain change. The following variables were not associated with pain change: sex, income, social relationships, household composition, sedentary behaviour, physical exercise, sleep problems, fatigue, depression, general health, physical and mental quality of life. Only the significant variables were included in the multivariable model. The multivariable model on the imputed data showed that, after adjustment, age, education level, and pain at baseline were significantly associated with pain change (Figure 3).

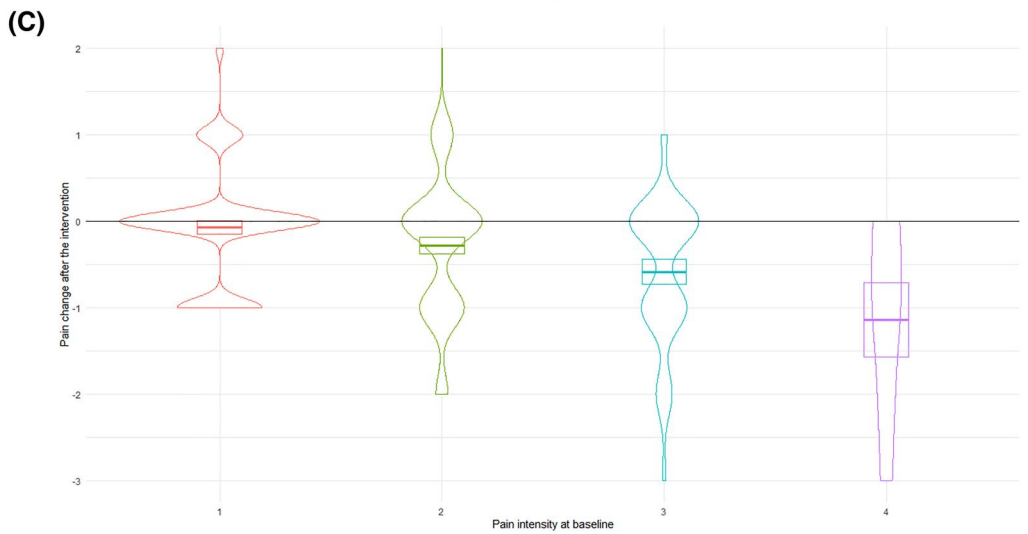
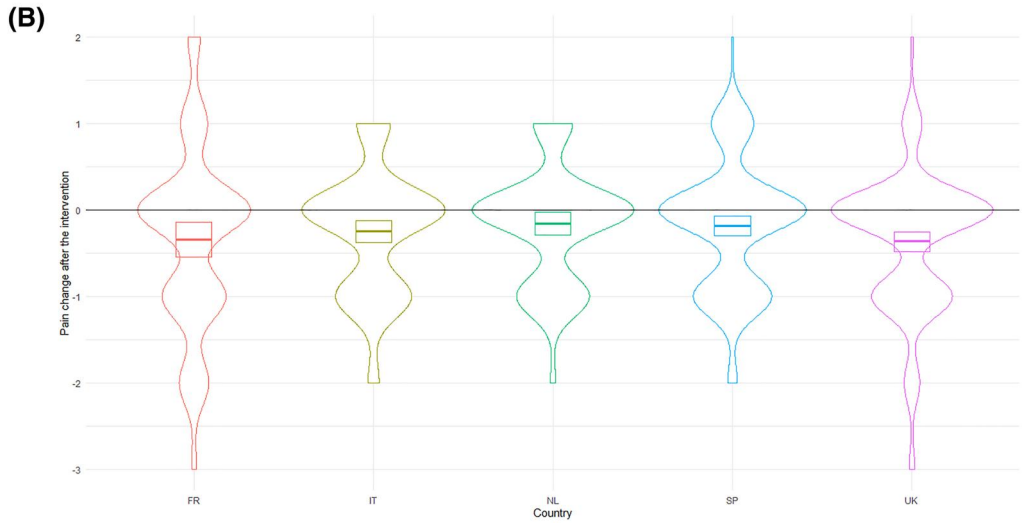
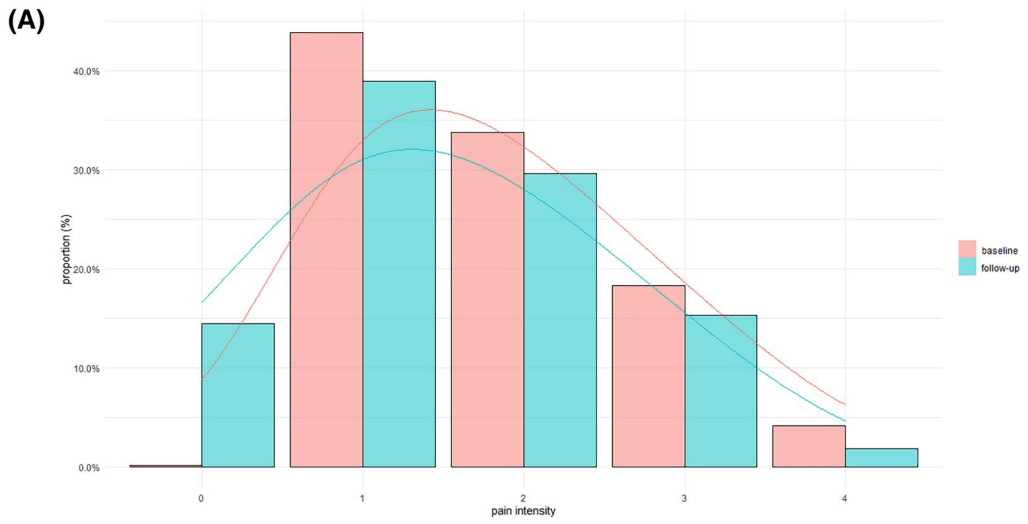
Pain decreased more in younger participants, for those with a higher education level, and for those whose initial pain was greater.

Complete cases analyses gave similar results (Supplementary Figure S2).

3.4 | Factors influencing the probability of a decrease in pain intensity

We also compared participants whose pain intensity decreased after the programme (responders, $N = 237$ in complete cases, $N = 368$ in imputed data) with those whose pain intensity stayed the same or increased (non-responders, $N = 470$ in complete cases, $N = 702$ in imputed data).

Univariable logistic regressions on imputed datasets ($N = 1070$) showed that age, education, country, and pain at baseline were significantly associated with the probability of an improvement. The multivariable model on the



imputed data showed that, after adjustment, age, education, and pain at baseline were significantly associated with the probability of a pain decrease (Supplementary Figure S3). Younger participants were more likely to respond, as well as those with a higher education level, and those experiencing more pain at baseline.

4 | DISCUSSION

4.1 | Conclusion

Our results therefore support the idea that a training programme is able to improve pain management and alleviate the consequences of chronic pain on the quality of life, including in vulnerable populations. This study was the first to investigate how pain was modified after the CDSMP intervention in vulnerable populations, using a multicentric protocol in five countries (France, Italy, Spain, The Netherlands, United Kingdom).^{68,69} Six months after the beginning of the intervention, the intensity of pain was significantly lowered ($p < 0.0001$). Complete cases analyses and analyses on imputed datasets gave similar results. Our analyses allowed adjusting for a wide range of variables (sex, age, education level, income, social relationships, household composition, physical exercise, sedentarity, fatigue, sleep problems, physical and mental quality of life, depression, self-reported health).

4.2 | Limitations

Some studies have shown a benefit of the self-management programs for pain,^{41,70} although other studies did not find such effect on pain.^{32,70,71} Many of these studies had a low sample size with about a hundred participants. In this regard, our study is exceptional with a sample size of almost a thousand individuals at follow-up, despite the high attrition rate. Younger and less educated participants were more likely to be lost, as well as those who generally had less social relationships. Therefore, evaluating the benefits of the intervention appeared challenging at first glance. However, thanks to the development of imputation methods, we were able to take into account the issue that the data were probably not missing at random.

Overall, our analyses have shown the potential for the CDSMP intervention to have a beneficial effect on pain. However, the effect size was rather weak (Cohen's D around 0.3). The amplitude of the behavioural changes obtained with health education programs in vulnerable populations can be limited, because adverse socio-economic conditions implies constraints that limit individual's capacity for adopting health-promoting behaviours. For example, while the prevalence of smoking is higher among low socio-economic individuals, the desire to quit does not differ greatly according to socio-economic status, nor does health literacy about the risks of smoking.⁷²

The main limitation of this study is the lack of a control group, preventing from any definitive conclusion. We cannot strictly affirm that the intervention was beneficial: it is indeed possible that participants who experienced lower levels of pain at follow-up had used various pain managing strategies, including strategies that had not been taught in the workshops (such as yoga or meditation), or that they benefitted from other workshops or educational programs. Another potential explanation is that the mere participation in a study and the social interactions induced have resulted in a decrease in pain. It is even possible that pain spontaneously decreased over the 6 months. The existence of an asymmetric regression to the mean effect cannot be excluded either.

Moreover, the absence of data after the 6 months follow-up measurement prevents from investigating any long-term effect of the intervention. The persistence of the benefits on pain intensity needs to be investigated.

FIGURE 2 Raw data. (A) Pain at baseline and follow-up, for participants who reported pain at baseline (raw data); (B) pain change in each country (raw data); (C) pain change (i.e. pain intensity at follow-up minus baseline) as a function of pain intensity at baseline (raw data).

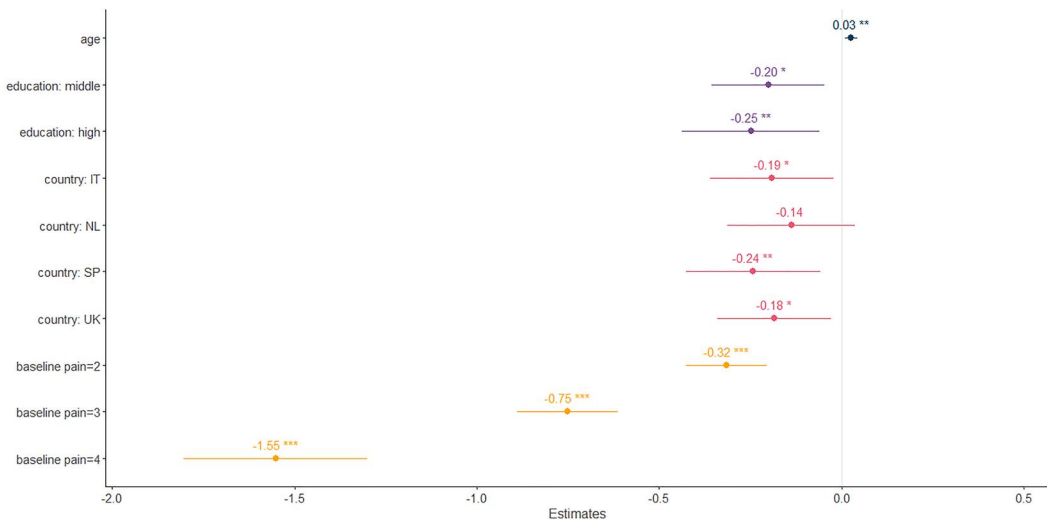


FIGURE 3 Result of the multivariable linear model with pain change as the outcome, using imputed data. Estimate values are represented with 95%CI and significance level (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Negative estimate = pain has decreased after the intervention. The variables that are not represented were not included because not significant in a univariable model.

Finally, some useful information are missing, such as the type of chronic condition (articular, digestive, metabolic, etc.), the height and weight of participants (as these variables can have an influence on pain), their ethnic/cultural background, the type of vulnerability (e.g. social isolation vs. economic deprivation), and the use of painkillers during the study (which is also a potential confounder). Further research should specifically address these points to be able to demonstrate the relevance of CDSMP interventions for chronic pain, and the specific questions related to vulnerability need to be more thoroughly investigated.

4.3 | Practice implications

The significance of employing the CDSMP in vulnerable patients with chronic pain is conclusively established for the first time in a large sample study. Prior studies relied on small samples and yielded conflicting results. Additionally, this study stands as the first investigation showing the CDSMP's effectiveness in improving pain symptoms within vulnerable populations. Despite being those who require such interventions the most, these populations have been understudied until now.

Predictive factors for improved efficiency include a younger age and higher education level. Consequently, education programs of this nature should specifically target these groups, with potential adjustments required to cater to other demographics.

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CONFLICT OF INTEREST STATEMENT

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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