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Effectiveness of a home-based nursing support and cognitive restructuring intervention on the quality of life of family caregivers in primary care: A pragmatic cluster-randomized controlled trial ☆,☆☆

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ABSTRACT

Background: Caregivers of patients with chronic conditions or disability experience fatigue, burden and poor health-related quality of life. There is evidence of the effectiveness of support interventions for decreasing this impact. However, little is known about the benefits of home-based nursing intervention in primary health care.

Objectives: To evaluate the effectiveness of a home-based, nurse-led-intervention (CuidaCare) on the quality of life of caregivers of individuals with disabilities or chronic conditions living in the community, measured at 12-month follow-up.

Methods: A pragmatic, two-arm, cluster-randomized controlled trial with a 1-year follow-up period was performed between June 2013 and December 2015. Consecutive caregivers aged 65 years or older, all of whom assumed the primary responsibility of caring for people with disabling conditions for at least 6 months a year, were recruited from 22 primary health care centers. Subsequently, 11 centers were randomly assigned to usual care group, and 11 were assigned to the intervention group. The caregivers in the intervention group received the usual care and additional support (cognitive restructuring, health education and emotional support). The primary outcome was quality of life, assessed with the EQ-5D instrument (visual analog scale and utility index score); the secondary outcome variables were perception of burden, anxiety, and depression. Data were collected at baseline, at the end of the intervention, and at the 6- and 12-month follow-up visits. We analyzed the primary outcome as intention-to-treat, and missing data were added using the conditional mean single imputation method.

Results: A total of 224 caregivers were included in the study (102 in the intervention group and 122 in the usual care group). Generalized Estimating Equation models showed that the CuidaCare intervention was associated with a 5.46 point (95% CI: 2.57; 8.35) change in the quality of life, as measured with the visual analog scale adjusted for the rest of the variables at 12 months. It also produced an increase of 0.04 point (95% CI: 0.01; 0.07) in the utilities. No statistically significant differences were found between the two groups at 12 months with respect to the secondary outcomes.

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Conclusions: The findings suggest that incorporating a home-based, nurse-led-intervention for caregivers into primary care can improve the health-related quality of life of caregivers of patients with chronic or disabling conditions.

What is already known

- Caregivers play a central role in caring for individuals with disabilities who are living in the community.
- Anxiety, depression, perception of burden and poor health-related quality of life are frequently reported symptoms in caregivers.
- Research shows that there are a variety of effective interventions to reduce these symptoms, but there is limited knowledge regarding the impact of home-based, nurse-led interventions in primary care on caregiver's outcomes.

What this paper adds

- The results of the CuidaCare study suggest that a home-based, nurse-led intervention in primary care improves the health-related quality of life of caregivers of patients with chronic conditions or disability.
- This improvement in health-related quality of life is maintained over time.
- Further research is needed on the cost-effectiveness and implementation strategies of home-based, nurse-led interventions in health systems.

1. Background

According to data from United Nations, the number of older persons has increased substantially in recent years, and that growth is projected to accelerate in the coming decades (Department of Economic and Social Affairs, 2015).

At the same time, the prevalence of chronic diseases is increasing (World Health Organization, 2018). Multimorbidity is the norm for people with chronic disease, and it is associated with worse physical and mental health, functional impairment and increased disability (National Institute for Health and Care Excellence, 2019).

The appropriate management of such long-term disorders is the main challenge facing health care systems worldwide (World Health Organization, 2018). New chronic care models emphasize community care (University of Birmingham, 2009). In Spain, the Estrategia para el Abordaje de la Cronicidad del Sistema Nacional de Salud (Ministerio de Sanidad - Servicios Sociales e igualdad, 2012) considers home the best place for the care of people with disabilities. This transfer of responsibility means that caregivers play a key role in maintaining the health of people with chronic or disabling conditions. Family or informal caregivers are individuals who have a personal relationship with and provide unpaid assistance to individuals who have a chronic or disabling condition (Family Caregiver Alliance, 2014).

Caregivers have a range of needs in relation to their caregiving role and in the maintenance of their own health and self-care (Grant and Graven, 2018; McCabe et al., 2016), and they highlight the needs for tools, skills and opportunities to address their mental health; greater emotional support; the maintenance of social relationships; and personal time for self-care (Tatangelo et al., 2018). The main outcomes reported by caregivers in studies assessing the impact of long-term caregiving are poor health-related quality of life, perception of burden, stress symptoms, and anxiety (Corry et al., 2015; Duggleby et al., 2016a; Jensen et al., 2015; Parker et al., 2008; Ploeg et al., 2017; Thomas et al., 2017; Williams et al., 2016).

Systematic meta-reviews assessing caregiver support for people with chronic illness conclude that interventions should be aimed at empowering the caregiver to continue in their care role while maintaining an optimal level of self-care and managing their own health (Corry et al., 2015; Thomas et al., 2017). Tatangelo and McCabe propose that the needs and perceptions of caregivers should be considered in the design of support strategies that involve health-promotion activities among caregivers (Tatangelo et al., 2018).

A review including eight systematic reviews of studies assessing the effectiveness of interventions for caregivers of people with chronic illness, suggests that support programs, educational interventions and active information increase caregivers' competence for care, improve their quality of life and decrease depression and burden, while psychological interventions have no effect on family functioning or on the competence of the caregiver (Corry et al., 2015). A meta-analysis of clinical trials evaluating educational interventions for caregivers of people with dementia shows low effects on quality of life, depression, and level of burden (Jensen et al., 2015).

Recent Cochrane reviews related to caregiver support agree that the nature of the interventions, the professionals and settings in which they are carried out are very heterogeneous and that studies with higher methodological quality, longer follow-up time and better descriptions of the professionals involved and settings in which the studies were developed are needed (Corry et al., 2019; Liu et al., 2018; Treanor et al., 2019). The evidence for caregiver support interventions is very limited in the primary care setting. In the Spanish National Health System, the general practitioners and nurses have a list of assigned patients and attends to all their health needs and problems, whether they are treated at the health-care center or at the patient's home. Also, the nurses who assume responsibility for the formal care of community-dwelling people with disabilities implement different caregiver support strategies. The aim of this study was to assess the effectiveness of the CuidaCare nursing intervention to improve the quality of life of caregivers compared to usual care in primary care measured at 12-month follow-up. As secondary objectives, we measured the impact of the CuidaCare intervention on perception of burden, anxiety and depression.

2. Methods

2.1. Design

This work was designed as a pragmatic, multicenter, two-arms, cluster-randomized controlled trial lasting one year. It was performed in the primary health care setting. The healthcare centers were the randomized clusters. The CONSORT checklist is available as supporting information (Supplement 1).

The study was registered at ClinicalTrials.gov (NCT 01478295). Methodological details can be found in the study protocol (Rico-Blázquez et al., 2014) (Supplement 2).

2.2. Setting and study population

Twenty-two healthcare centers in five municipalities of the Madrid region (Madrid City, Alcalá de Henares, Torrejón de Ardoz, Torres de la Alameda and Meco) that had an assigned population of 549,203 and a home care portfolio service for people with disabilities (functional impairment, neurocognitive disorders, elderly, advanced chronic diseases such as heart failure or chronic obstructive pulmonary disease, cancer, osteoarticular disease and palliative care needs) were selected if they had at least one nurse interested in voluntarily participating in the study. The characteristics of the healthcare centers and the 89 nurses involved in the study are showed in Supplement 3 Characteristics of the primary healthcare centers and nurses by study group.

Caregivers were aged 65 years or older, all assumed the primary responsibility for caring for people with disabling conditions at least 6 months a year and were able to participate in the study. They were recruited between February 2014 and May 2014. Caregivers already receiving therapeutic intervention to decrease their burden or caring for nursing home residents/hospitalized people during the recruitment period were excluded.

2.3. Randomization and masking

The nurses identified, from among the patients assigned to their list, those caregivers who could be included in the study during routine nursing consultations at the health center or at home visits. They offered caregivers to participate consecutively and requested their informed written consent to participate before healthcare centers randomization.

The 22 healthcare centers were assigned by randomization to the usual care group or the CuidaCare intervention group by an independent statistician who was masked to the healthcare centers' identifiers using Epidat 3.1 software. Random allocation was stratified by center size and done in blocks of two, with intervention and usual care allocated simultaneously.

Because of the nature of the intervention, neither the caregivers nor the nurses were blinded. Outcome data were collected by nurses who were aware of the allocations. Analysis was performed by the research team, which was blinded to allocation.

2.4. Sample size

The study was designed with 80% power and α value of 0.05 to detect a relevant post-intervention average difference of 15 points on the visual analogue scale and an standard deviation of 25 (Roset et al., 1999) between the two groups. The minimum sample size was corrected for the design effect, contemplating an intracluster coefficient of 0.022 (Adams et al., 2004) and a mean cluster size of 15 caregivers. The final simple size required was 142 caregivers (71 by group), assuming a 20% loss to follow-up. It was estimated a minimum of 11 clusters.

2.5. Intervention

In the control group, caregivers' health problems were addressed in a nursing consultation following the usual practice of monitoring acute or chronic illnesses in primary care, without taking into account the factors associated with informal care that cause stress, overload and morbidity. During the design and development of the trial, there was no specific protocol in the primary care service for caregivers.

In the intervention group, the caregivers received the usual practice and an additional support, the CuidaCare intervention. CuidaCare is an intervention that aims to improve the quality of life of caregivers through improved coping and self-efficacy, not only to care for the people with disabling conditions but also to care for oneself. It is a complex intervention (Campbell et al., 2007) based on the Dorothea Orem theory. The Nursing Outcomes Classification and Nursing Interventions Classification were used as the basis its component activities (Johnson et al., 2007; NANDA International and Herdman, 2012). It incorporates cognitive restructuring techniques, health education and emotional support. A multidisciplinary team of family nurses and psychologists designed it. The nurses underwent a previous 4-hour training activity. The intervention was performed by the nurse of each patient at the home that the caregiver shared with the dependent person. The intervention was structured as six visits lasting 30 minutes each; the visits occurred monthly, and a reinforcement session was provided at 6 months. Additionally, the caregivers received an informative pamphlet with information to reinforce the content addressed in each session. Supplement 2 describes both arms of the study as currently recommended (Perera, R; Heneghan,C; Yudkin, 2007).

2.6. Data collection and outcomes

The primary outcome was quality of life, which was measured using the EQ-5D-3L instrument. The EQ-5D is a valid generic instrument that measures quality of life with a visual analogue scale (range: 0 to 100; higher ratings indicate higher quality of life) and five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Health states are converted into a weighted utility index score (full health has a value of 1, and death has a value of 0). We collected scores for the five dimensions and the utility index score according to the method proposed for our country (Herdman et al., 2001).

We also defined the secondary variables as follows: perception of burden, measured using the Caregiver Strain Index; anxiety, measured using the Goldberg Anxiety Inventory; and depression, measured using the Yesavage Geriatric Depression Scale.

Additionally, we collected data about age, gender, marital status, familiar relationship and educational level of the caregiver and person with disabilities; living and caregiving conditions; formal support; and family function (family Apgar). Finally, we also recorded data on multimorbidity, performance in activities of daily living (Barthel scale), and cognitive disorder (Pfeiffer test) for the people with disabling conditions.

Outcomes were collected and recorded in an electronic data notebook at baseline, at the end of the intervention, at the 6 and 12-month follow-up. All variables were assessed at all time points, except for sociodemographic variables, which were collected only at baseline.

For the nurses, age, gender, professional experience in primary care, and caregiver support training level were collected. For the health centers, the total assigned population, the population aged 65 years or older and number of patients included in the home care service were collected.

2.7. Statistical analysis

A descriptive analysis (means, medians, frequencies of distribution) was performed for the primary health care centers and for the characteristics of the nurses, caregivers and people with disabling conditions in each study group. In addition, we compared the baseline characteristics of the participants who completed the follow-up assessments (completers) and those who were lost to follow-up (drop-out).

The results for the primary outcomes were analyzed on an intention-to-treat basis. Two methods of handling missing data of main outcome were used: the last observation carried forward method and conditional mean imputation (Salim et al., 2008). A

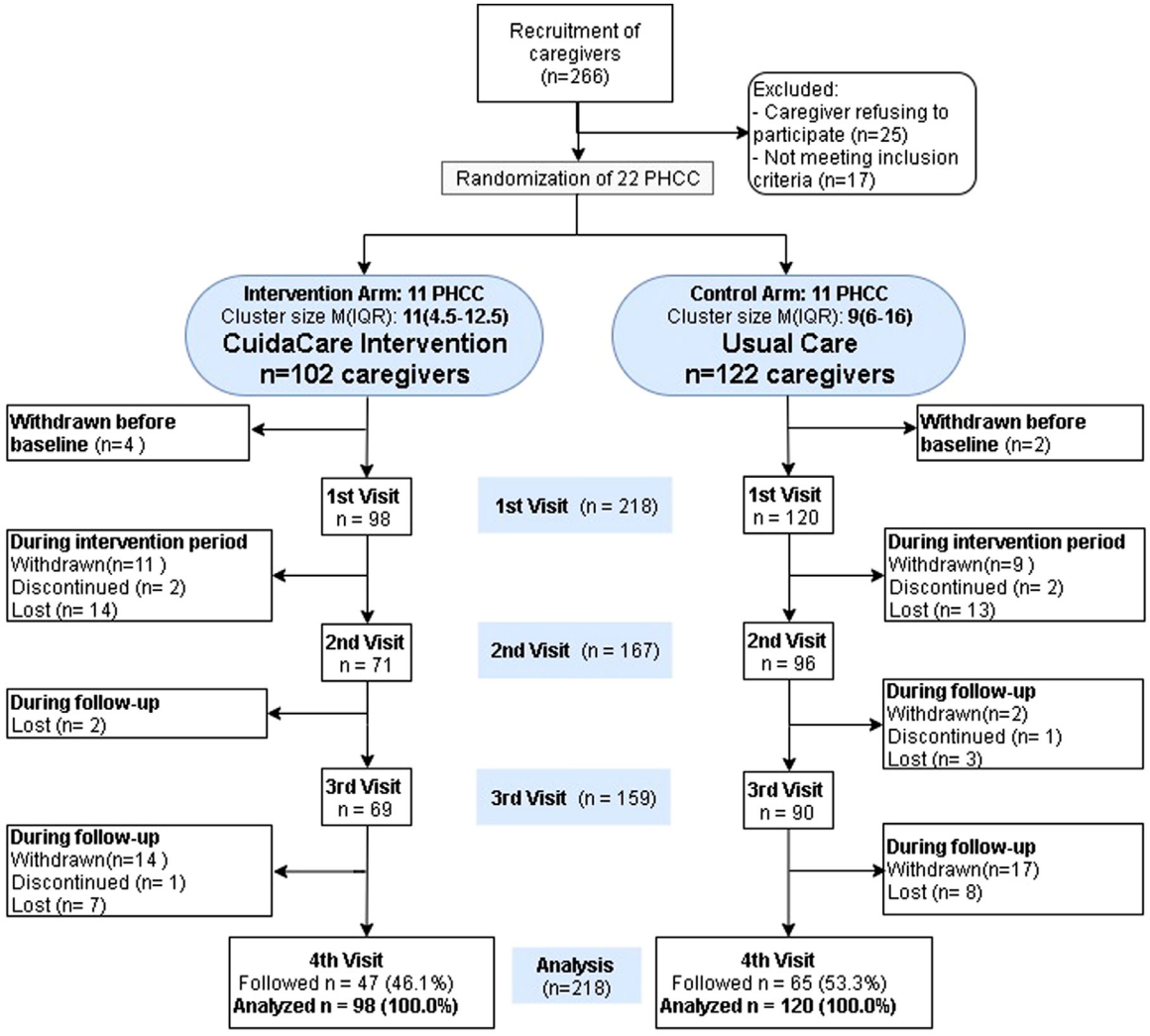

Fig. 1. Flow diagram of participants.

sensitivity analysis was performed to compare the output from both imputation sets.

Although the initial design proposed using multilevel mixed models to study the effect of cluster on quality of life scores, after verifying in the empty model that the variability explained by healthcare centers was less than 4% and taking into account that the main response variable had an asymmetric distribution and those a priori assumptions could not be made regarding the distribution of variance, we decided to analyze the factors associated with the change in the caregiver's quality of life, as measured by the visual analogue scale and the index score at the 12-month follow-up, Generalized Estimating Equation models were performed. This model takes into account the nonindependence of the measurements at the different visits in the parameter estimation and obtains unbiased estimators of the associations in the presence of heteroscedasticity (Jones, 2012). Identity links and normal or gamma distributional families were used in the study of the explanatory factors for the improvement in quality of life.

We analyzed the secondary outcomes according to group. Missing values for perception of burden, anxiety and depression were added using the last observation carried forward approach. Significance was set at $p<0.05$. All analyses were performed using STATA 14 software.

2.8. Ethics approval

All participants (caregivers and nurses) provided written informed consent. The study was approved by Comité Ético de Investigación Clínica del Hospital Príncipe de Asturias and the Comisión Central de Investigación de la Gerencia Asistencial de Atención Primaria de Madrid.

3. Results

Between February and May 2014, we approached a total of 266 caregivers for participation; the final study sample included 224 caregivers (122 in usual care group and 102 in CuidaCare group). The baseline visit in June 2014 was completed by 218 caregivers. The last follow-up visit (12 months) was completed by 112 (50%) caregivers. The percentage of losses was slightly higher in the experimental group (53.9% vs 46.7%). The death of the individual with disability or his/her transfer to a long-term care home

was main reason for dropout (49.1%), followed by a change in the nurse's position after passing the public health service examination (21.7%). The 9.2% of the losses were related to the caregivers (16% had an illness that limited their ability to continue as a caregiver, 7.5% had a change of residence, and 5.7% left the study). Fig. 1 shows the flow diagram for the caregivers in each group, and those remaining at the data collection point, according of the CONSORT-Cluster Group.

3.1. Participant characteristics

A total of 72.8% of the caregivers were women; the mean (SD) age was 78.1 years (6.9), and 148 (66.1%) were living alone with people with disabling conditions. The median (IQR) experience as a caregiver was 6 years (3-10). Eighty-two caregivers (36.6%) received some formal support, with a median (IQR) of 8.5 (4.5 - 31.5) hours of domestic help per week. The mean (SD) visual analogue scale score was 56.8 (21.6), and the utility index score was 0.68 (0.29). One hundred two (46.8%) caregivers reported perception of burden, 118 (54.1%) had positive anxiety test score, and 28 (12.9%) had positive depression test score.

No relevant differences were found between the intervention and control groups at baseline for any of the outcomes variables, except the index mean. At baseline, the outcome variables between caregivers who had completed the study (completers) and those who had discontinued (dropouts) were similar.

Table 1 shows the sociodemographic and clinical characteristics of the caregivers by study group and dropout status.

The average age for people with disabling conditions was 82.9 years (12.6) and 90.1% had two or more chronic conditions. 58.7% had cognitive disorders and more than 20% presented total or severe dependency for performance activities of daily living. Supplement 4 shows characteristics of people with disabling conditions by study groups and drop-out status.

3.2. Primary outcome

In the intention to treat analysis with the conditional mean imputation method, at the end of the intervention the difference in mean visual analogue scale changed by -11.28 (95% CI: -15.60; -6.95); and at the 12-month follow-up, it changed by -15.76 (95% CI: -21.33; -10.20). Regarding utilities, the difference between groups at the end of the intervention was -0.14 (95% CI: -0.20; -0.07) and -0.17 (95% CI: -0.26; -0.09) at the 12-month follow-up. Note that a negative difference denotes improvement in the CuidaCare group with respect to the control group.

The intention to treat and by-protocol analyses at the different times of measurement of the primary outcome, as well as the sensitivity analysis of both imputation methods, are shown in Table 2.

In the intention to treat analysis, the change in the visual analogue scale score was -12.84 (95% CI: -16.26; -9.43) in female caregivers and -17.26 (95% CI: -22.23; -12.29) for male caregivers ($p = 0.000$). Regarding the change in utilities, there was a change of -0.17 for female caregivers (95% CI: -0.22; -0.12) ($p = 0.000$) and -0.06 for male caregivers (95% CI: -0.12; 0.003) ($p = 0.06$) (Fig. 2).

In the intention to treat analysis, the factors associated with changes in the visual analogue scale and index scores (from baseline to the 12-month follow-up) are presented in Fig. 3 and Supplement 5.

The intervention improved the mean visual analogue scale score by 5.46 (95% CI: 2.57; 8.35). At each visit, an average increase of 1.25 (95% CI: 0.46; 2.04) was found. Male caregivers improved on average of 5.63 (95% CI: 2.30; 8.96) points more than female caregivers, and for each person living in the home with the caregiver and the dependent person, the caregivers' average perceived quality of life improved by 2.38 points (95% CI: 1.19; 3.57). The factors that negatively affected the visual analogue scale score were receiving domestic help; family dysfunction; and the perception of anxiety, depression and/or burden.

The intervention improved the mean utilities score by 0.04 (95% CI: 0.01; 0.07). Other factors that explained a positive change in the utilities included gender, with men improving 0.10 (95% CI: 0.06, 0.13) points more than women on average; household size, for each person living in the home with the caregiver and the dependent person, the caregivers' average index improved by 0.02 points (95% CI: 0.004; 0.027); cognitive disorders of dependent person improved on average of 0.03 (95% CI: 0.003; 0.062) and total or severe dependence of the dependent person, which was associated with a 0.06 change (95% CI: 0.022; 0.093). The caregivers' average perceived quality of life decreased by 0.004 points (95% CI: -0.005; -0.002) for every year they spend caring for.

Given the exploratory nature of the study and the aim of facilitating the clinical interpretation of the results, a "success" variable was calculated by defining three clinically relevant cutoff points in the improvement of the quality of life, namely, improvements of 5, 10 and 15 points on the visual analogue scale at the end of the intervention and at the 6- and 12-month follow-ups, respectively. Supplement 6 shows the impact of the intervention (intention to treat analysis with conditional mean imputation). To improve the quality of life measured with the visual analogue scale at the end of the intervention by at least 15 points, the relative risk was 3.06 (95% CI: 1.65; 5.65), with an number needed to treat of 4.85 (95% CI: 3.20; 9.99). To maintain this improvement at 12 months of follow-up, the relative risk was 3.24 (95% CI: 1.98; 5.29), and the number needed to treat was 3.14 (95% CI: 2.33; 5.07).

3.3. Secondary outcomes

The per protocol and intention to treat analyses with last observation carried forward imputation found no evidence of difference between the intervention and usual care groups with respect to the secondary outcomes of anxiety, depression and burden perception. Supplement 7 shows the changes in these outcomes over time.

4. Discussion

4.1. Main findings of the study and comparison with other studies

The CuidaCare intervention was associated with significant improvements in quality of life measured with visual analogue scale at the end of the intervention and at the 6- and 12-month follow-up visits before adjusting for any influencing variables. In the adjusted models, an increase of 5.46 points in the visual analogue scale score was observed at the 12-month follow-up. The index score also improved discretely and significantly at all study visits, and the effect remains in the fitted model.

The CuidaCare intervention incorporates cognitive restructuring techniques, health education and emotional support, techniques that have demonstrated effectiveness for improving caregiver-reported outcomes such as subjective well-being, burden, depression and quality of life (Corry et al., 2015; Jensen et al., 2015; Liu et al., 2018; Treanor et al., 2019). In a systematic review (Amador-Marín and Guerra-Martín, 2017) of thirteen studies of nonpharmacological interventions to improve the quality of life of caregivers of people with Alzheimer's disease, five found favorable results with psychotherapeutic, multicomponent, formative and community interventions; three of these studies used the EQ-5D as a measurement instrument, although two of them only considered the visual analogue scale score. Corry et al. conducted a

Table 1
Sociodemographic and clinical characteristics of caregivers by study group and dropout status

Characteristics	Total (n =224) n (%) Mean (SD) Median (IRQ)	Intervention group (n = 102) n (%) Mean (SD) Median (IQR)	Control group (n = 122) n (%) Mean (SD) Median (IQR)	*p*	Completers (n = 112) n (%) Mean (SD) Median (IQR)	Drop out (n = 112) n (%) Mean (SD) Median (IQR)	*p*
Age	78.1 (6.9)	77.5 (6.7)	78.5 (7.2)	0.275	78.0 (7.1)	78.1 (6.8)	0.930
Gender, female	163 (72.8%)	80 (78.4%)	83 (68%)	0.082	81 (72.3%)	82 (73.2%)	0.881
Marital status				0.171			**0.056**
Married	192 (85.7%)	91 (89.2%)	101 (82.8%)		101 (90.2%)	91 (81.3%)	
Single/divorced/widowed	32 (14.3%)	11 (10.8%)	21 (17.2%)		11 (9.8%)	21 (18.7%)	
Familiar relationship				0.525			0.139
Spousal	160 (71.4%)	75 (73.5%)	85 (69.7%)		85 (75.9%)	75 (67.0%)	
Ancestor/descendant/other	64 (28.6%)	27 (26.5%)	37 (30.3%)		27 (24.1%)	37 (33.0%)	
Educational level				**0.000**			0.081
Primary or less (≤12 years)	156 (69.6%)	84 (82.3%)	75 (59.0%)		84 (75.0%)	72 (64.3%)	
Secondary or above (>12 years)	68 (30.4%)	18 (17.7%)	50 (41.0%)		28 (25.0%)	40 (35.7%)	
Employment status				**0.008**			**0.005**
Homemakers (unpaid domestic work)	78 (34.8%)	45 (44.1%)	33 (27.1%)		49 (43.8%)	29 (25.9%)	
Employed/unemployed/retired	146 (65.1%)	57 (55.9%)	89 (72.9%)		63 (56.2%)	83 (74.1%)	
Living conditions							
Living with care recipient only, (yes)	148 (66.1%)	67 (65.7%)	81 (66.4%)	0.911	76 (67.9%)	72 (64.3%)	0.572
Household size	2 (2-3)	2 (2-3)	2 (2-3)	0.963	2 (2-3)	2 (2-3)	0.273
Caregiving conditions							
Experience as a caregiver (years)	6 (3-10)	6 (3-11)	6 (3-10)	0.373	7 (3-10.5)	5 (3-10)	0.248
Family function (Family Apgar), (dysfunction)	55 (25.2%)	28 (28.6%)	27 (22.5%)	0.305	26 (23.2%)	29 (27.4%)	0.481
Dependency law							
Level recognized by government (yes)	65 (29.0%)	33 (32.3%)	32 (26.2%)	0.315	32 (28.6%)	33 (29.5%)	0.883
Formal support (yes)	82 (36.6%)	34 (33.3%)	48 (39.3%)	0.352	38 (34%)	44 (39.3%)	0.405
Domestic helper (yes)	72 (32.1%)	25 (24.6%)	47 (38.6%)	**0.025**	37 (33%)	35 (31.3%)	0.775
Domestic helper (hours per week) (n=72)	8.5 (4.5-31.5)	7.5 (4-18)	10 (6-40)	0.239	10 (4-35)	8 (5-28)	0.853
Outcome variables	(n=218)	(n = 98)	(n = 120)		(n = 112)	(n = 106)	
Health-related quality of life (EQ-5D)							
VAS (mean (SD))	56.8 (21.6)	54.9 (23)	58.4 (20.4)	0.247	54.9 (20.1)	58.8 (23)	0.182
VAS (median, IQR)	51 (48-70)	50 (40-75)	60 (50-70)	0.217	50 (46-70)	60 (50-76)	0.131
EQ-Index (mean (SD))	0.68 (0.295)	0.63 (0.327)	0.72 (0.261)	**0.030**	0.67 (0.283)	0.69 (0.307)	0.508
EQ-Index (median, IQR)	0.82 (0.58-0.89)	0.74 (0.32-0.89)	0.83 (0.65-0.89)	0.083	0.75 (0.53-0.89)	0.83 (0.60-0.89)	0.074
Burden (Caregiver Strain Index) (yes)	102 (46.8%)	45 (45.9%)	57 (47.5%)	0.816	53 (47.3%)	49 (46.2%)	0.871
Anxiety (Goldberg) (yes)	118 (54.1%)	55 (56.1%)	63 (53%)	0.593	63 (56.2%)	55 (51.9%)	0.518
Depression (Yesavage) (yes)	28 (12.9%)	17 (17.4%)	11 (9.2%)	0.073	14 (12.5%)	14 (13.2%)	0.876

Table 2
Changes in primary outcomes over time, within and between the Cuidacare and control groups. Per protocol and intention to treat analyses

Primary outcomes	Analysis	Baseline (V1)		End of intervention (V2)					6 month follow-up (V3)					12 month follow-up (V4)				
		n, mean (SD)		n, mean (SD)		Difference in means (95% CI) within groups[b]		Unadjusted difference between groups[b,c] (95% CI)	n, mean (SD)		Difference in means (95% CI) within groups[b]		Unadjusted difference between groups[b,c] (95% CI)	n, mean (SD)		Difference in means (95% CI) within groups[b]		Unadjusted difference between groups[b,c] (95% CI)
		CuidaCare	Control	CuidaCare	Control	CuidaCare	Control		CuidaCare	Control	CuidaCare	Control		CuidaCare	Control	CuidaCare	Control	
VAS-EQ-5D[a]	PPT	n=98 54.9 (23)	n=120 58.4 (20.4)	n=71 64.2 (20.8)	n=96 56.4 (17.4)	9.46 (6.06; 12.87)	-0.67 (-3.31; 1.98)	-10.13 (-14.35; -5.91)	n=69 67.9 (19.6)	n=90 55.9 (18.4)	12.25 (7.68; 16.82)	-0.64 (-4.02; 2.73)	-12.89 (-18.4; -7.38)	n=47 66 (19.7)	n=65 53.7 (16.8)	12.04 (6.26; 17.82)	-1.94 (-6.24; 2.26)	-13.98 (-20.95; -7.01)
	ITT-LOCF			n= 98 61.8 (21.3)	n=120 57.8 (18.8)	6.86 (4.26; 9.45)	- 0.53 (-2.65; 1.58)	-7.39 (-10.68; -4.1)	n= 98 63.8 (21.3)	n=120 57.8 (19.5)	8.81 (5.42; 12.2)	-0.57 (-3.09; 1.96)	-9.37 (-13.5; -5.25)	n= 98 63.5 (21)	n=120 57.2 (19.5)	8.57 (5.16; 11.98)	-1.18 (-3.69; 1.33)	-9.75 (-13.88; -5.63)
	ITT-CM			n= 98 64.2 (17.3)	n=120 56.4 (15.4)	9.29 (5.95; 12.63)	-1.99 (-4.83; 0.84)	-11.28 (-15.6; -6.95)	n= 98 67.9 (16.1)	n=120 55.9 (15.8)	12.96 (8.89; 17.04)	-2.44 (-5.70; -0.81)	-15.41 (-20.53; -10.29)	n= 98 66 (13.3)	n=120 53.7 (12.2)	11.69 (6.8; 15.35)	-4.69 (-8.36; -1.02)	-15.76 (-21.33; -10.2)
EQ-5D-Index[a]	PPT	n=98 0.63 (0.327)	n=120 0.72 (0.261)	n=71 0.74 (0.242)	n=96 0.69 (0.279)	0.10 (0.04; 0.17)	-0.01 (-0.05; 0.02)	-0.12 (-0.19; -0.05)	n=69 0.75 (0.217)	n=90 0.69 (0.244)	0.11 (0.03; 0.19)	0 (-0.04; 0.05)	-0.11 (-0.19; -0.02)	n=47 0.76 (0.264)	n=65 0.67 (0.295)	0.14 (0.03; 0.25)	-0.03 (-0.09; 0.03)	-0.17 (-0.29; -0.54)
	ITT-LOCF			n= 98 0.71 (0.272)	n=120 0.71 (0.275)	0.08 (0.03; 0.12)	-0.01 (-0.04; 0.02)	-0.09 (-0.14; -0.03)	n= 98 0.71 (0.257)	n=120 0.72 (0.243)	0.08 (0.02; 0.13)	0 (-0.03; 0.03)	-0.08 (-0.14; -0.01)	n= 98 0.72 (0.278)	n=120 0.70 (0.291)	0.09 (0.02; 0.15)	-0.01 (-0.05; 0.22)	-0.10 (-1.17; -0.03)
	ITT-CM			n= 98 0.74 (0.201)	n=120 0.69 (0.247)	0.11 (0.05; 0.16)	-0.03 (-0.06; 0.00)	-0.14 (-0.20; -0.07)	n= 98 0.75 (0.178)	n=120 0.69 (0.209)	0.11 (0.05; 0.18)	-0.02 (-0.06; 0.01)	-0.14 (-0.21; -0.07)	n= 98 0.76 (0.178)	n=120 0.67 (0.211)	0.12 (0.05; 0.19)	-0.05 (-0.1; -0.00)	-0.17 (-0.26; -0.09)

[a] Quality of life. Euroqol 5D. In VAS and Index, higher scores indicate better Health-related Quality of Life PPT = analysis per protocol ITT_LOCF=analysis per intention to treat. Missing data replace using Last Observation Carried Forward ITT-CM= analysis per intention to treat. Missing data replace using Conditional mean imputation

[b] Compared to baseline

[c] Diff= (mean control group) - (mean CuidaCare group). A negative difference denotes more quality of life in CuidaCare group than control group.

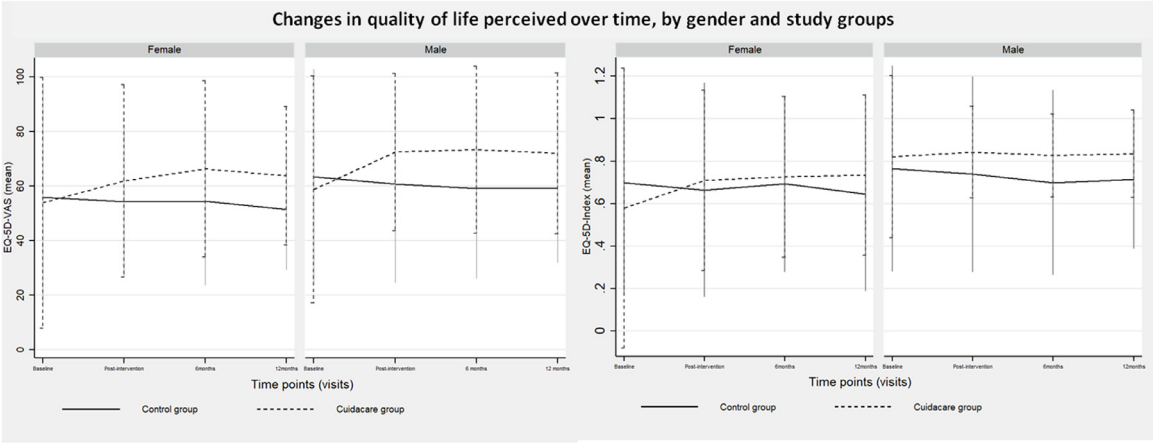

Fig. 2. Changes in quality of life perceived over time, by gender and study groups.

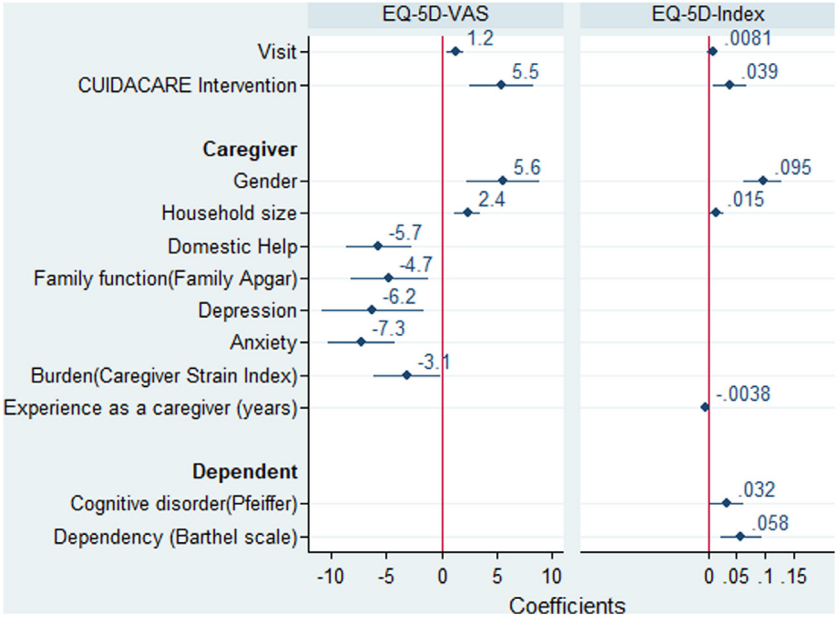

Fig. 3. Factors associated with changes in Quality of Life (EQ-5D-VAS and EQ-5D-Index) at 12 months follow-up.

systematic review of systematic reviews of interventions to support caregivers of people with selected chronic conditions and concluded that there was evidence that education and support programs improved caregiver quality of life (Corry et al., 2015). Along the same lines, but evaluating psychosocial interventions, Treanor et al. conducted a systematic review of 19 studies that included 3725 caregivers and concluded that compared to usual care, psychosocial interventions may slightly improve caregiver quality of life immediately post intervention but may have little to no effect on caregiver quality of life at 12 months (Treanor et al., 2019). In comparison, the CuidaCare intervention maintained improvement at one year of follow-up.

However, it is not easy to compare its impact on quality of life with the results of other studies. The most recent updated systematic reviews (Corry et al., 2015; Jensen et al., 2015; Lenferink et al., 2015; Thomas et al., 2017) of trials of caregiver support interventions show heterogeneity in terms of the interventions, settings, inclusion criteria, outcomes, and effects. The results are mixed and inconclusive. A systematic review and meta-analysis of randomized controlled trials to assess whether educational programs for caregivers of individuals with dementia living in the community are effective for improving caregiver burden, quality of life, depression and transitions to long-term care settings compared with usual care conclude that the effect on quality of life is not appreciable, as the studies varied in their reporting of subdomains and constructs within scales (Jensen et al., 2015).

Unlike other interventions, CuidaCare does not seem to have an effect on burden, anxiety, or depression. In the recent meta-analysis of Walter and Pinquart (Walter and Pinquart, 2019), which included 282 controlled studies and aimed to evaluate the effectiveness of different types of interventions on caregivers caring for people with dementia, psychoeducational and multicomponent interventions had small-to-moderate effects on the caregiver's ability/knowledge, subjective well-being, burden, depression, and anxiety, whereas the efficacy of other intervention types was domain-specific.

The factors that are strongly associated with an increase in quality of life are male gender and not living alone with the dependent person, while the presence of signs and symptoms of anxiety, depression, burden, or family dysfunction were associated with a lower perceived quality of life. These results are concordant and have been widely described in previous studies of factors

related to quality of life (Casal Rodríguez et al., 2019; Du et al., 2017; Duggleby et al., 2016b; González-de Paz et al., 2016; Mosquera et al., 2018; Mosquera Metcalfe et al., 2019). This gender difference in self-perceived health between male and female caregivers could reflect differences in the general population, in which women generally report a lower quality of life, and may not be specific to female caregivers (Crespo M, 2007).

In our study, having domestic help significantly decreased quality of life. The presence of secondary caregivers, both professional and informal, has been associated with lower quality of life in our setting. The study by Casal et al. conducted in Spain (Casal Rodríguez et al., 2019), which studied the factors that determine the quality of life of caregivers of people with Alzheimer's disease, observed that caregivers who needed support in the home to provide care and technical assistance had a lower average quality of life than caregivers who did not need help (index scores of 0.08 vs 0.09). This same effect is reflected in the updated meta-review by Sian Thomas et al., which aimed to update what is known about effective interventions to support those who care for ill, disabled or older adults and obtained similar results. This study concluded that the effectiveness of respite care remains a paradox, given the apparent conflict between the empirical evidence and the views of caregivers (Thomas et al., 2017).

In our study, the number of years the caregiver has provided care, decreased the quality of life, but other care-related factors, such as or the amount of time that the dependent person attends day centers, were not associated with the caregiver's quality of life. In a country-wide, population-based study in Spain that used 2011-2012 Spanish National Health Survey data and aimed to measure the impact of disease, health-related habits, and risk factors associated with informal caregiving; although that study did not explore quality of life, it found no association between the number of hours of informal care per week, the number of years the caregiver had provided care, or the amount of time spent providing care and some of our secondary outcomes, such as depression and burden.

4.2. Strengths and limitations

One of the greatest limitations is related to the 50% loss to follow-up at one year. To analyze its possible impact on the quality of the study, we performed complementary analyses. Baseline characteristics were compared between the caregivers who complete the study and those who were lost, and the only difference found was in the level of education. The caregivers who dropped out of the study had obtained a higher level of education (secondary or higher vs. primary/no education). However, the effect of the intervention identified in the per-protocol analysis was maintained in the ITT analysis with both imputation by last observation carried forward and imputation by the conditional mean. Although losses were slightly higher in the experimental group, as shown in the results, only 5.7% of the caregivers left the study for personal reasons. The fact that the intervention was developed in their home limited no adherence and the intervention was well accepted by the caregivers. Acceptability on the part of the nurses was explored with a questionnaire and showed a high level of satisfaction with the development of the CuidaCare intervention.

Among the strengths of the study are its pragmatic approach and the methodological rigor with which it was conducted. According to the PRECIS tool, the study was highly pragmatic (Ka Shing et al., 2015), studying the effectiveness of the CuidaCare intervention in real-world clinical practice. To this end, the study had the broad participation of clinical nurses (89 professionals), who recruited the caregivers directly from the primary health care centers where they were treated. On the other hand, all caregivers were included in the study, regardless of the characteristics of the dependent person in their care (e.g., the severity of their dependence or the disease that caused dependence), and this heterogeneity of caregivers permitted a view that was not restricted to a specific disease.

Conditioned by the pragmatism of the study, the protocol was modified. The sample size was recalculated to reconsider the number of caregivers that the same nurse could include according to his or her workload at the start of the study. Under the sample size calculation assumptions defined in the protocol (NCT01478295. https://ClinicalTrials.gov), an average cluster size of 15 was considered; this was smaller than the initial cluster size and resulted in a new sample size of 142 caregivers, with 71 in each group (Rico-Blázquez et al., 2014).

The trial was rigorously conducted. Its design followed the Cochrane Reviews recommendations, which highlight the need to design studies of high methodological quality, with a long follow-up time and a good description of the professionals and settings for which they were developed (Corry et al., 2019; Liu et al., 2018; Treanor et al., 2019); additionally, the recommended standards for cluster randomized trials were followed (Campbell, 2012). This occurred within the framework of translational research through an independent study in the field of primary care, as suggested by experts (Dadich and Hosseinzadeh, 2013).

Additionally noteworthy is the design, which used patient-reported outcome measures as the main outcome variable. This is further highlighted by the fact that the results were of importance to the caregivers involved. Measuring the impact of the intervention in terms of quality of life emphasizes the importance of incorporating the perspective of the affected individuals themselves in the provision of care.

In addition, the 12-month follow-up showed that the impact of CuidaCare was maintained over time, with a 11.6 points increase in the visual analogue scale (CI95% 6.8, 15.3) for the intervention group compared with their scores at the beginning of the study.

In our context, it was essential to focus on caregivers over 65 years of age. Although this limits the generalizability of the results to the global population of caregivers, it is strength since people over 65 years of age are the ones who most often serve as caregivers for dependent people who live in the community. In addition, in the descriptive studies that led to this study, caregiver role strain was the most common nursing diagnosis in the medical history of people in this age group.

The differences found in the baseline comparison in the mean of the index disappear when median score are considered and are explained by some extreme values of the distribution and not by differences between groups. The differences in education level and the presence of domestic help can be explained by the effect of cluster randomization; one of the randomized centers serves a population with a very high socioeconomic level, unlike the other centers. The fact that this health center was randomly assigned to the control group means that these differences influenced the final effectiveness of the intervention, contrary to the study hypothesis.

5. Implications of the study findings

In summary, the findings of this study show that a home-based nursing intervention in primary care improves the quality of life of caregivers of dependent people living in the community.

The CuidaCare intervention can easily be integrated into usual care. The intervention does not require additional human or technical resources; it is simply a reorientation of services and, ultimately, an investment in health promotion and disease prevention at the first level of care.

The evaluation of the effectiveness of the CuidaCare intervention is an important step for family and community nursing, devel-

oping and testing practices that strengthen evidence-based practice.

CuidaCare could be a focus of future nursing research in supporting caregivers of people with multiple chronic conditions in primary care.

Author contributions

Trial Management Committee: MRB (principal investigator), EEM, IdCG, and TSC conceived the study and participated in its design and coordination.

Technical Support Group: ARA, CGP, LDP, LMdRM, MAC, MBCS, MCCA, MEZ, MMM, MSdFR, NHdV, PGS, and RMGQ participated in the different phases of intervention design and the development of the research.

Clinical Investigators at Primary Health Care Centers (CuidaCare Group): collected the data for the study, which included recruiting caregivers, collecting informed consent, applying the interventions, collecting data, and arranging and performing follow-up for caregivers.

Statistical analysis: MRB, IdCG, JARL, MMM, and JCGM.

Writing Committee: MRB, IdCG, and JARL wrote the manuscript; MRB, IdCG, JARL, TSC, PGS, MMM, ARA, MAC, and MSdFR reviewed it. All authors in the CuidaCare Group read and approved the final manuscript. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

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Conflict of Interest

The authors declare that they have no conflicts of interest regarding the aims of this study. The funders had no role in study design, collection, analysis, or interpretation of the data or in the writing of the report or the decision to submit the paper for publication.

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Supplementary materials

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