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Original

EFECTOS Y COSTE-EFECTIVIDAD DE UNA INTERVENCIÓN A TRAVÉS DE INTERNET PARA CUIDADORES FAMILIARES DE ENFERMOS CON DEMENCIA: METODOLOGÍA DE UN PROGRAMA DE EJERCICIO PERSONALIZADO

EFFECTS AND COST-EFFECTIVENESS OF AN INTERNET-BASED INTERVENTION FOR FAMILY CAREGIVERS OF PATIENTS WITH DEMENTIA: METHODS OF A PERSONALIZED EXERCISE PROGRAM

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RESUMEN

Objetivos: La demencia representa una prioridad de salud pública, dada la creciente prevalencia de la enfermedad y el elevado número de cuidadores que atienden a los pacientes. Así, la tarea de cuidado produce un impacto físico, psicológico y social en los cuidadores, lo que puede generar implicaciones sociales y económicas sobre los sistemas sanitarios. Se han desarrollado diferentes intervenciones basadas en el ejercicio para ayudar a los cuidadores a hacer frente a esta situación, sin embargo, los cuidadores familiares, generalmente presentan limitaciones para hacer ejercicio físico con regularidad, debido a la falta de tiempo y/o porque residen lejos de las instalaciones convencionales, especialmente los que viven en entornos rurales. Este estudio pretende describir en profundidad una nueva metodología para el desarrollo de un ensayo controlado aleatorio, el cual evaluará la eficacia y el coste efectividad de un programa de ejercicio físico personalizado a través de Internet para mejorar el estado físico y la calidad de vida relacionada con la salud de las cuidadoras de familiares con demencia. Métodos: La intervención incluirá tres sesiones de ejercicio físico de una hora de duración por semana durante tres meses y a través de Internet; será supervisada por un entrenador personal y se realizará en el domicilio de la cuidadora, con interacción en tiempo real. Resultados: Los resultados esperados serán: 1) viabilidad y adherencia al programa; 2) efectos positivos en el estado físico y la calidad de vida relacionada con la salud; 3) menor riesgo de depresión; 4) disminución de la sobrecarga subjetiva y 5) reducción de otros síntomas psicológicos. Los análisis también incluirán la evaluación de la eficacia en función de los costes de la intervención. Discusión: Esta intervención personalizada podría ser una estrategia eficaz para superar las limitaciones de las cuidadoras para participar en un programa de ejercicio físico. Asimismo, esta intervención podría ser una propuesta factible y adecuada para reducir el impacto físico y psicológico que subyace de su función como cuidador primario, y podría ser un programa de asistencia innovador y coste-efectivo para esta población. Conclusión: Esta intervención podría proporcionar soluciones a los responsables de desarrollar las políticas sanitarias para promover la aplicación de servicios de atención sanitaria vía Internet a nivel regional y nacional, y así reducir la demanda de recursos de atención de la salud presencial por parte de las cuidadoras.

Palabras clave: Ejercicio físico, Internet; cuidador familiar; coste-efectividad; calidad de vida; condición física; sintomatología psicológica; sobrecarga.

ABSTRACT

Objectives: Dementia depicts a public health priority, given the increasing prevalence of the disease and the elevated number of caregivers who provide care for patients. Thus, the caregiving task produces a physical, psychological and social impact on caregivers, which can generate social and economic implications on health care systems. Different exercise-based interventions have been developed to help caregivers to cope this situation, however, family caregivers are often limited to do physical exercise regularly due to lack of time and/or they reside away from conventional facilities, especially those who live in remote rural locations. This study aims to describe comprehensively a new methodology for a randomized controlled trial that will evaluate the efficacy and cost-effectiveness of a personalized Internet-based physical exercise intervention to improve the fitness and health-related quality of life of female family caregivers of relatives with dementia. Methods: The intervention will include three Internet-based 1-hour-long physical exercise sessions per week for 3 months; it will be supervised by a personal trainer, and it will be performed at the caregiver's home by using online interaction in real-time. Results: The expected outcomes will be: (1) feasibility and adherence to the intervention; (2) positive effects on fitness and health-related quality of life; (3) lower risk of depression; (4) decrease in subjective burden and (5) reduction of other psychological symptoms. Analyses will also include the evaluation of the cost-effectiveness of the intervention. Discussion: This personalized intervention could be an effective strategy to overcome the limitations of caregivers to participate in a physical exercise program. Moreover, this intervention could be a feasible and appropriate approach to reduce the underlying physical and psychological impact of their role as a primary caregiver, and could be an innovative and cost-effective assistance program for this population.

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Conclusion: The present intervention might provide policymakers with potential solutions to promote the implementation of Internet-based care services at regional and national level, lessen caregivers' demands for face-to-face health-care resources.

Keywords: physical exercise; Internet; familiy caregiver; cost-effectiveness; quality of life; fitness; psychological symptoms; burden.

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INTRODUCTION

Dementia represents a public health priority, as the prevalence of people who suffer from this disease has increased dramatically in recent years, with the appalling social and economic implications that entail for the health care systems (Alzheimer's Association, 2020). Over 50 million people live with dementia, and the number of new patients diagnosed each year reaches approximately 10 million. Following this trend, the number of patients with dementia will be over 74 million and 131.5 million in 2030 and 2050, respectively (Prince et al., 2015), thus increasing significantly the number of elderly dependent people worldwide (World Health Organization, 2019). Therefore, it is expected that the demand for caregivers to provide dement patients with care will also increase dramatically in the world (Birkenhäger-Gillesse, Kollen, Zuidema, & Achterberg, 2018). There are two kinds of caregivers, namely formal and informal caregivers. While formal caregivers are those who are paid to give care, such as doctors, nurses, social assistants, etc., informal caregivers are not paid to provide care. Informal caregivers are usually members of the family (Alzheimer's Association, 2020; Badia, Lara, & Roset 2004; Erol, Brooker, & Peel, 2015), mostly the spouse or the daughter, who often lives at the care recipient's home (Badia, Lara, & Roset, 2004; Erol et al., 2015). Caregiving-related responsibilities are often assumed by women due to the traditional gender role of home-tasks developing covered by a woman. The majority of female caregivers tend to cover the caregiving tasks and also to develop the home activities or even to work, which depicts an overburden in her daily life. Given the unexpected nature of this role, caregivers are prone to experience diverse physical, psychological, social and financial difficulties (Bauer, Koepke, Sterzinger, & Spiessl, 2012; Chiao, Wu, & Hsiao, 2015; Collins & Swartz, 2011; L. Fredman, Bertrand, Martire, Hochberg, & Harris, 2006), that negatively impact on their health-related quality of life (HRQoL) (Ho, Chan, Woo, Chong, & Sham, 2009; M. Lee, Ryoo, Crowder, Byon, & Wiiliams, 2020). Regarding the consequences for their physical health, they are very diverse (Dawood, 2016; Del Rio Lozano, Garcia-Calvente, Calle-Romero, Machon-Sobrado, & Larranaga-Padilla, 2017; Flores, Jenaro, Moro, & Tomsa, 2014; Garzón-Maldonado et al., 2016; Gusi et al., 2009). Informal caregivers use to show higher levels of hypertension and other cardiovascular-related disorders (C. J. Farran et al., 2016; S. Lee, Colditz, Berkman, & Kawachi, 2003), as well as limited aerobic capacity in comparison with non-caregivers (C.J. Farran et al., 2016). Moreover, they also suffer from severe back pain due to deficiencies in the trunk muscle strength (Badia, Lara, & Roset, 2004; Gusi et al., 2009), and other musculoskeletal ailments (CEAFA & Sanitas, 2016). From a psychological perspective, these caregivers report high levels of overburden, distress and other psychological alterations, such as anxiety and depression (Chiao et al., 2015; Delgado et al., 2014; Gustaw, Beltowska, & Makara-Studzinska, 2008; Haines, Denehy, Skinner, Warrillow, & Berney, 2015; Pérez-Fuentes, Gázquez, Ruiz, & Molero, 2017; Pinquart & Sorensen, 2003). Moreover, they usually show other symptoms, such as emotional strain, hostility, discomfort, irritability, and disinhibition (Arthur, Gitlin, Kairalla, & Mann, 2018; Birkenhäger-Gillesse et al., 2018; Cooper, Selwood, Blanchard, & Livingston, 2010; Feast, Orrell, Russell, Charlesworth, & Moniz-Cook, 2017; Franco, Sola, & Justo, 2010). Concerning financial and social difficulties, informal caregivers usually spend the most of their economic resources in the costs arising from the care-related responsibilities, and spend the majority of their time with the care-recipient, this situation limiting significantly their leisure activities and, consequently they can feel social isolation (Bramboeck, Moeller, Marksteiner, & Kaufmann, 2020; Salazar, Murcia, & Solano 2016).

A wide variety of non-pharmacological interventions conducted to alleviate the adverse effects of the caregiving-related responsibilities on informal caregivers' health and quality of life has been described in previous reports. In this sense, psychoeducational programs, support groups, community-based programs, counselling and other multicomponent approaches have shown positive effects (Alzheimer's Disease International, 2016; Bartfay & Bartfay, 2013; Gaugler & Kane, 2015; Martin-Carrasco et al., 2014; Sorensen, Pinquart, & Duberstein, 2002). In addition, physical exercise-based interventions have also shown effectiveness and feasibility to improve informal caregivers' HRQoL (Castro, Wilcox, O'Sullivan, Baumann, & King, 2002; Cuthbert et al., 2018; C. J. Farran et al.,

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2016; Hirano et al., 2011; Lok, Lok, & Canbaz, 2017), as well as physical and mental health status in the care recipient (Mollinedo, Lopez, & Cancela-Carral, 2019). Outcomes of these interventions often improve caregivers' fitness level (Cuthbert et al., 2018), increase their physical activity level (C.J. Farran et al., 2016; C. J. Farran et al., 2016; Hirano et al., 2011), and reduce fatigue and subjective burden (Castro, Wilcox, O'Sullivan, Baumann, & King, 2002; Hill, Smith, Fearn, Rydberg, & Oliphant, 2007; Hirano et al., 2011; Lowery et al., 2014; Orgeta & Miranda-Castillo, 2014). The exercise-based methods of these interventions are diverse and include endurance exercise (King, Baumann, O'Sullivan, Wilcox, & Castro, 2002); walking (Loi et al., 2014; Lowery et al., 2014); yoga (Lavretsky et al., 2013; Waelde, Thompson, & Gallagher-Thompson, 2004) or multicomponent exercise-based activities (Hill et al., 2007). However, only a few interventions have been conducted following an RCT approach (C.J. Farran et al., 2016), which are usually limited, in turn, by the sample size (Chan et al., 2016). Therefore, the results of these studies shall be interpreted with caution. Besides these limitations, these studies show also a great diversity in relation to variables, such as physical exercise intensity, the weekly number of sessions, length of the intervention and kind of exercise, which also limits the generalization of the results to larger groups (Jackson & Browne, 2017; Lamotte, Shah, Lazarov, & Corcos, 2017; Orgeta & Miranda-Castillo, 2014). Moreover and, in accordance with Pagan-Ortiz et al., (2014), the interventions that are individually-tailored and are offered face to face considering participants' time preferences generate more positive effects (Pagan-Ortiz, Cortes, Rudloff, Weitzman, & Levkoff, 2014). In fact, informal caregivers often prefer interventions at a distance due to their caregiving responsibility (Cristancho-Lacroix et al., 2013). In this sense, previous research has reported evidence that web-based interventions improve mental health and wellbeing in caregivers of patients with dementia (Parra-Vidales, Soto-Perez, Perea-Bartolome, Franco-Martin, & Munoz-Sanchez, 2017; Ploeg et al., 2017). Moreover, the use of technology in health-focused interventions has grown in recent years (Sherifali et al., 2018). Thus, the development of Internet-based interventions may represent a new suitable strategy to support informal caregivers efficiently, as they usually have limited leisure time and have difficulties to leave their home due to the caregiving-related duties (Hopwood et al., 2018). Previous research that has analyzed the effectiveness of Internet-based programs in respect of improving caregivers' health has reported promising results (Cristancho-Lacroix et al., 2013; Ploeg et al., 2017; Sherifali et al., 2018), as they may offer efficiency, they are less economically demanding and may be easily available to caregivers at their own homes (Ploeg et al., 2017; Zhao et al., 2019), especially to those caregivers who are living in remote and/or rural areas (Eysenbach, 2001). Moreover, informal caregivers are usually limited when it comes to attending conventional facilities, such as sport centers or sports clubs. In addition, the long distances to these conventional facilities as well as the low supply of personalized physical exercise programs in small and/or rural municipalities make caregivers not to get involved in regular physical exercise interventions (Hopwood et al., 2018).

On the other hand, RCT-based studies analyzing the cost-effectiveness of Internet-based exercise interventions aimed at primary informal caregivers of relatives with dementia are scarce (Nickel, Barth, & Kolominsky-Rabas, 2018; Zhao et al., 2019). Regarding the particular case of Spain, the Spanish public sanitary or welfare system lacks interventions that are based on the use of interactive programs at a distance delivered through the Internet at caregivers' home. Therefore, RCTs-based studies particularly aimed at evaluating the cost-effectiveness and the impact of personalized Internet-based physical exercise interventions on primary informal caregivers' physical and psychological status -quality of life- shall be promoted (Domingues, Verreault, & Hudon, 2018). Positive results of these interventions may represent a remarkable strategy to develop future health care policies focused on the promotion of Internet-based health care services that are more accessible and less expensive (Blom, Bosmans, Cuijpers, Zarit, & Pot, 2013). Therefore, the present study aims to describe a protocol for the evaluation of the cost-effectiveness and the effects of a personalized Internet-based physical exercise intervention on female family caregivers' quality of life, that is, on physical and mental health. Our hypothesis is that the addition of an Internet-based

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face-to-face exercise program for informal caregivers of patients with dementia is feasible, effective (health-related quality of life and fitness and mental health) and cost-effective alternative compared to usual care.

1.1. Ethical Considerations

This study has been ethically reviewed and approved by The Ethics Committee of the University of Extremadura (Approval number: 7/2010). Study participants will be required to sign a written informed consent prior to participation in the study.

1.2. Trial Registration

National Health Institute (UK) ISRCTN Registry: ISRCTN15450537, Registered 28 April 2020 https://doi.org/10.1186/ISRCTN15450537.

METHODS

Study Design

The present study poses to research the effect of an exercise program similar in load to these described in a previous research developed by our research group (Madruga, Prieto, Rohlfs, & Gusi, 2020), but adapted and delivered by means of Internet-based technology instead of the previous in-person face-to-face delivered at patient's home. As some of the participants will complete the intervention program -intervention group- and others will not -control group-, the present protocol study follows a between-subject experimental design.

Regarding the present study protocol, a RCT-based design will be employed to evaluate the cost-utility of an Internet-based physical exercise intervention with duration of 3 months. The study will be supervised by the principal investigator of the research project, N.G., who is MSC in Health Economics and Pharma-economy. Participants of the study will be randomly allocated to either the Internet-based exercise group (intervention group) or the non-exercise group (control group). Assessment will be performed at baseline (pre-intervention assessment), 3 months after the intervention (post-intervention assessment) and 12 months after the intervention (post-intervention follow-up assessment); see Figure 1. The study will be conducted in accordance with the updates of the Declaration of Helsinki.

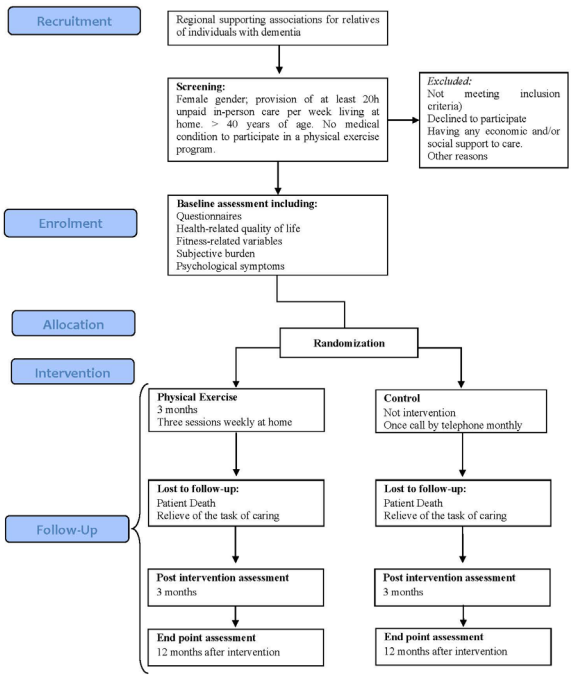

Figure 1: Flow chart of participants

Figure 1. Flow chart of participants
Nota. Table attached in annex

Participants

Potential participants will be recruited from associations of relatives of people with dementia. Participants will be screened according to eligibility criteria, that is, inclusion and exclusion criteria by the research team. In accordance with the previously published protocol (Madruga, Prieto, et al., 2020), the inclusion criteria will be: voluntarily willing to sign the informed consent to participate in the study; being female caregiver of a relative with dementia; living together with the care recipient; providing the relative with dementia with at least 20 hours of unpaid in-person care per week; being age 40 years or older; having no medical condition that could limit participation in a moderate-intensity physical exercise program; not having participated in any regular physical activity program, that is, having been engaged in more than two 20-minutes-long sessions of physical exercise per week during the 6 months prior to the intervention; not having changed the

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medication or doses of medication for at least 3 months prior to the study, in case of prescribed medication; and not having plans to move from the place of residence within the 12-months-long study. Moreover, additional criteria will be also required regarding participant's home, namely availability of an Internet connection; having a laptop or personal computer equipped with a webcam, and a telephone. The exclusion criteria will be: having any external economic and/or social support to provide the patient with dementia with care.
Finally, a written letter explaining the conditions of the study will be sent to all potential participants, and possible doubts by the participants will be solved by the members of the research team before the recruitment.

Sample size calculation

The sample size will be estimated according to four main aspects: 1) The utility score of the Spanish version of the EQ-5D-3L questionnaire as primary outcome. 2) The consideration and considering that the experimental study follows a between-subject experimental design. In this sense, a significance level alpha = 0.05 and 80% of the statistical power are required to detect a minimal clinically significant difference of M= 0.20 and SD = 0.12 (Zijlstra, Braakman-Jansen, Taal, Rasker, & van de Laar, 2007). 3) The costs of the present intervention, which have to be added to the conventional treatment, provided by the public health system, will be estimated according to Spanish standards, 1130 € per caregiver in three months. This amount will include the personal trainer's salary (40 hours for sessions and assessment), insurance, travel-related costs, basic computer (200 €) and sport goods (50€) to follow the sessions and Internet provider fee. 4) Finally, the cost-efficiency ratio expressed as cost per quality-adjusted-life-years (QALYs). This parameter will range between 10,000 and 50,000 € per QALYs (Sacristan, Oliva, Del Llano, Prieto, & Pinto, 2002), and a conservative estimated sum = 30,000 € per QALYs will be used. A cost-efficiency ratio = 0.21 corresponds to a 0.06 QALYs. In view of the above, a sample size of n = 50 caregivers distributed in two groups—control group and intervention group—will be necessary to achieve a statistical power of 80% with a 95% of confidence interval, using an analysis of variance in parallel to parametric testing and anticipating a potential drop-out rate of 20%. In addition, the confidence interval will also be improved by using a bootstrapping technique.

Randomization

Randomization will be performed using a computer algorithm. This procedure will be done by an independent person of the research group, who will not participate in the evaluation process or delivery of the intervention nor know the hypothesis. In addition, participants' sociodemographic data and the data collected by means of questionnaires will be stored in a password-protected laptop. Indeed, we will use an individual system of codification that will be only accessible to some members of the research team.

Intervention

During the intervention, three Internet-based physical exercise sessions per week will be performed for each informal caregiver. Each session will last 1-hour and will be delivered at the caregiver's home and directed by a personal trainer, who will directly interact with the participant in real-time through a computer electronic application that enables a streaming interaction. Participants' physical performance at physical exercise sessions will be continuously supervised by the personal trainer. While the participant is performing the exercise session, the care-recipient may stay at home, either doing entertaining activities (e.g., watching TV) or carrying out appropriate handicrafts).
Regarding the physical exercises sessions, these will be similar to the previously described (Madruga, Prieto, et al., 2020). In particular, each physical exercise session will involve moderate-intensity aerobic exercises that range from 3 to 6 metabolic equivalents. Each session will consist of: (1) A warming-up block of 10-minutes by performing slight movements of progressive intensity and easy walks and steps. (2) Next, 10-minutes of aerobic exercise at 60–65% of maximal heart rate (HR_{max}). (3) Then, 20-minutes of overall mobility and strength exercises using the own body weight and materials, such as weights and elastic bands. (4) A further 10-minutes of aerobic exercise at 60–65% HR_{max} (5) The

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session will be completed with a 10-minutes-long carrying out cool-down activities that include low-intensity physical exercises for the recovery.
Participants´ heart rate will be continuously evaluated in order to monitor that they are doing well. For this purpose, caregivers will wear an individual small running computer (Polar S625X, 1 Polar Electro Oy, Kempele, Finland). During the 3-months-long intervention, and in order to promote additional healthy habits, participants of the intervention group will receive twice-weekly by e-mail a health-counselling that highlights several health-related issues for their daily lives, such as appropriate daily rest, safe positioning of the back while providing care, and regular participation in daily social activities.
On the other hand, participants of the control group will be instructed to continue their normal daily activities as well as not to be engaged in any new physical exercise intervention throughout the 3-months-long study period in order to avoid confounding results. During the intervention period, participants of the control group will be telephoned once a month in order to conduct an *ad hoc* standardized and non-exercise-related conversation with the personal trainer to remind them the conditions of the study.

Measures

A wide variety of physical and psychological variables will be assessed: health-related fitness variables (strength, endurance, flexibility, balance, and motor function); subjective burden, anxiety, depression, psychological symptomatology and global health-related quality of life. For this purpose, several appropriate fitness tests and questionnaires will be performed. All selected evaluation tools have been shown to have a moderate to high reliability and validity in samples of old people and caregivers.

Consistently to the methodology of the previous protocol published (Madruga, Prieto, et al., 2020), all participants will be assessed by trained staff of the research team at participants' home at baseline and 3 months after the intervention. Each evaluation will last 45 minutes. Prior to the baseline evaluation, the evaluators will participate in an assessment-training workshop that consists of 3-4-hours-long 3 sessions, aimed at improving evaluators' skills to apply the protocol accurately. The evaluators will also be instructed to implement the questionnaires, and they will be trained to perform the selected fitness tests and to proceed with the participants. In particular, they will learn how to perform the exercise sessions in a small room instead of a sport facility and how to talk to caregivers to prevent them to provide the care recipients with care during the session). These training sessions will also be supervised by the head of the research team. In addition, the evaluators will be given a testing manual that has been written *ad hoc* by the research team to apply a standardized evaluation protocol. This manual details the particular assessment procedures.

General measures.
An *ad hoc* made questionnaire will be used to compile participants' socio-demographic data as well as the characteristics of the care provided by them. The compiled demographic data will include age, place of residence, marital status, number of co-residents at home, educational level, smoking and alcohol consumption habits, and level of physical activity. Additional data will include the nature of the relationship with respect to the relative with dementia, and the number of years spent caring that relative.
Regarding the relatives with dementia, their level of independence will be assessed using the Barthel Index (Mahoney & Barthel, 1965). This tool evaluates care-recipients' ability to perform ten primary activities of daily living (Avargues-Navarro et al.), such as eating, bathing/washing and dressing, among others. Each of these activities is scored according to whether the care-recipient is able to do the activity independently. The total score of those ten activities will provide a quantitative estimation of the individual's level of independence, ranging from 0 to 100. Higher scores indicate greater levels of independence, and lower scores indicate the otherwise.

Analysis of the Effects of the intervention
During the intervention, data regarding participants' use of public and private health services will be registered. This information will include hospital admissions, use of medication and primary and

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secondary health appointments (e.g., nurse, doctors or social workers).

For an in-depth description of the evaluation procedures of all variables, readers are kindly referred to read Madruga et al. (2020).

Outcomes

Health-related quality of life and cost-utility

The analyses are essentially focused on the assessment of the cost-effectiveness of the Internet-based intervention, which is a complementary program to conventional care treatment. Thus, the primary outcome will be the Spanish time trade-off utility of EQ-5D-3L (EQ-5D-3L utility) in terms of QALYs. The EQ-5D-3L (Herdman, Badia, & Berra, 2001) will be used to assess participants' general health status and quality of life -physical plus mental health- on the basis of five dimensions: (1) mobility, (2) self-care, (3) daily activities, (4) pain and discomfort, and (5) anxiety and depression. Each dimension ranges from 1 to 3 according to a Likert scale, where 1 = no problem, 2 = some problems and 3 = extreme problems. Using a combination of these different dimensions, a total of 243 possible health states can be identified. After this screening, a total score of utility, which ranges from 1 = fully functional quality of life to 0 = death, will be obtained (Badia, Roset, Monserrat, Herdman, & Segura, 1999). Regarding participants' QALYs scores, its collection during and after the intervention will allow us to compare the impact of the intervention between the intervention and the control group. In addition, a 12-months-long follow-up period will be included, thus following the recommendations of the National Health Service (NHS). To avoid potential bias, data will be adjusted for differences in baseline EQ-5D-3L scores via regression analysis (Manca, Hawkins, & Sculpher, 2005).

Cost-utility: Cost units

Given that the physical exercise program is Internet-based, the direct societal costs of the intervention such as the travel expenses or the time spent by the caregiver at home will be reduced. However, the number of health-related visits to physician or nursery may vary. Nevertheless, variation of the travel costs derived from the initial visit to check and ensure the correct functioning of the Internet devices and to assess caregivers' quality of life -physical and mental health-, as well as the salary of the physical trainer will be included in the sensitivity analysis. Following the recommendations by the National Institute for Clinical Excellence (NICE) in the UK when it comes to making decisions regarding health-related policies, these economic analyses will be carried out from a health service perspective. This may help decide, whether the inclusion of the present program into the current health system should be funded. The targeted unit costs will be expressed in Euros (€) in the current year of intervention. Moreover, given the fact that the study will focus on effects observed over a period of ≤1 year, No adjustments will be required for changes in currency value over time. The expense derived from the present intervention will be calculated according to the following factors: standards on wages and working conditions of graduates; public-sector mileage; prices the cost of the private external management of the program, such as insurance, sport materials, etc.; health-care prices, such as consultations, etc., which will be stipulated on the basis of decisions by the regional government of Extremadura, and the drug prices, which will be based on the Spanish version of the Vademecum International (Vademecum).

Finally, HRQoL will be evaluated using the 15D questionnaire. This provides us with a generic, multidimensional, standardized, self-administered measure of health-related quality of life of participants by means of a single index score as well as a health profile (Sintonen, 2001). The questionnaire includes 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. For each dimension, there are five possible levels, which range from 1 -poor- to 4 -excellent-. The final score results from the sum of the points of all items of all dimensions of the questionnaire, and ranges from 13 -the worst- and 52 -the best-. Both the health profile and the index score vary between 0 and 1, which death and high HRQoL, respectively. Previous research has shown that a

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difference of 0.015 points in the index score from the 15D may represent a minimal clinically significant difference, for participants to perceive a difference (Alanne, Roine, Rasanen, Vainiola, & Sintonen, 2015).

Health status

To assess the physical and mental health state of participants, the validated Spanish version of the Short Form 36 health survey questionnaire (SF-36) will be used (Alonso, Prieto, & Anto, 1995). This questionnaire is a generic scale, which assesses health-related quality of life (Villagut et al., 2005). This questionnaire consists of 36 items and includes eight health-related subscales: physical functioning (PF), role limitations-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations-emotional (RE), and mental health (Covinsky et al.). For each subscale, and taking into account the Spanish normative reference for the general population, the resulting score ranges from 0 -worse health state- to 100 -best health state-. Its psychometric properties also produce two summary scores: While the sum of scores in first four subscales leads to the total score associated with the physical component, the sum of scores in last four subscales leads to the total score associated with the mental component.

Subjective burden

The Spanish version of the Zarit Burden Interview (ZBI) (Martin et al., 1996) will be used to assess caregivers' subjective burden. This is a 22-item self-report questionnaire that evaluates the burden that is experienced by caregivers. A single score is obtained according to a 0-to-88 points scale, where 0 indicates the least burden and 88 indicates the most severe burden (Zarit, Reever, & Bach-Peterson, 1980). Additionally, the questionnaire analysis evaluates the functional, psychological, behavioural, and economic limitations regarding relative the caregiving-related situation.

Depression

To assess the risk of depression, the Spanish version of the Short Form 15-item Geriatric Depression Scale (GDS) will be used (Izal & Montorio, 1994). This 15-item self-report questionnaire is a reliable screening-tool to detect major depression in the primary care setting. The total score ranges from 0 to 15 points (Yesavage, Brink, Rose TL., & Lum, 1983). Scores equal to or greater than 5 points may indicate the presence of depression (Shua-Haim, Haim, Shi, Kuo, & Smith, 2001).

Psychological symptomatology

To assess the psychological symptomatology by caregivers, the Spanish version of the Symptom Check List-90-R (SCL-90-R) will be used (Gonzalez de Rivera et al., 1989). It is a 90-item self-administered inventory aimed at evaluating psychological symptoms. In particular, the SCL-90-R includes nine primary symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism, as well as three indices for global distress. For each item, the resulted score rated by the participant on a range from 0 -not at all- to 4 -extremely- points in distress. The global severity index is, then, calculated as the average of the item scores, thus providing information about the perceived distress. This index is also used to evaluate the presence of psychological morbidity when the T scores of the global severity index or at least two primary dimensions are equal to or greater than 63 (Derogatis, 1977).

Fitness outcomes

In order to compare the resulting fitness outcomes of the present study with those from the previous study (Madruga, Prieto, et al., 2020), the methods to evaluate fitness will be similar. In particular, we will calculate or evaluate the following parameters:

- Body mass index (BMI) and waist/hip ratio (WHR) according to the recommendations established by the European Council (Oja & Tuxworth, 1995).
- Handgrip strength in both hands using a hand dynamometer (TKK; Tokyo, Japan).
- Flexor and extensor lumbar trunk muscle endurance using Ito-Shirado test (Ito et al., 1996).

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- Flexibility will be assessed using the sit-and-reach test (Wells & Dillon, 1952).
- Static balance will be assessed using the blind flamingo test (Rodriguez, Valenzuela, Gusi, Nacher, & Gallardo, 1998).
- Lower limb function by using the chair-stand test (Csuka & McCarty, 1985).

The description of the assessment procedures of these parameters, is in depth-detailed in Madruga et al., (2020, p. 9).

Exercise adherence.

A total of 36 online physical exercise sessions will be prescribed for caregivers in the intervention group during the 3 months of intervention. The personal trainer will monitor each session performed by participants. Exercise adherence rates during the study will be calculated as the percentage of the 36 prescribed exercise sessions that are actually completed.

Potential adverse effects of the intervention

Although the present physical exercise-based intervention will be adapted to participants' characteristics, a series of potential adverse effects should be considered. First, physical harm or injuries. In the case that the participant is seriously injured, the personal trainer will recommend the participant to visit her doctor. If the injury prevents the caregiver to continue with the intervention, we will recommend the caregiver to withdraw the intervention. Second, participants may feel resentful while performing physical exercises. In this case, the session might be suspended. Finally, due to caregivers' duties, the exercise session might also be occasionally interrupted.

Data statistical analysis

Student t-test for continuous variables and Pearson's chi-squared tests for categorical variables will be used to analyze possible inter-group differences at baseline. Moreover, the Kolmogorov-Smirnov test and the correction of Lilliefors will be used to test the normal distribution of variables. Inter-group differences will be analyzed using the Mann-Whitney U-test for continuous variables and the χ^2 test for categorical variables. An analysis of variance for repeated measures with Bonferroni adjustment will be performed to determine inter-group differences as a result of the intervention. In accordance with Hunter and Schmidt (2004) this analysis help increase precision of resulted data (Hunter & Schmidt, 2004). This analysis will be additionally adjusted for several potential mediator factors, such as age, subjective burden, care-recipients' Barthel Index, and length of caregiving-history at baseline. To determine the magnitude of the change, effect sizes for the standardized means differences between-groups will be calculated (Cohen, 1992). To elucidate the variables that best describe and predict the change in the assessed parameters, an adjusted multiple regression analysis will be performed. The significance level will be set at $p < 0.05$ for all tests. All statistical analyses will be performed using SPSS 22.0 (SPSS Inc. Chicago, USA). The cost-utility analysis will also use the updated Individualized Cost-Effectiveness Analysis (ICEA) CRAN package in R statistic program.

Cost-utility analysis

First, the individual incremental costs depicted previously of the addition of the Internet-exercise-based program compared to usual care, and the outcome changes measured in QALYs secondary to the intervention will be estimated using a health system view to assess health policymakers because the caregivers do not need to go out of home and they will be already at home for providing care. Second, the incremental cost-effectiveness ratio for the intervention will be calculated by dividing the mean incremental costs by the mean incremental QALYs. Thus, a cost-utility analysis will be performed. Third, plane plots of costs (X-axis) against the effects of health outcomes (Y-Axis) will allow a graphical analysis to elucidate if the intervention could be a cost-effective alternative and, right after, perform further analysis.

Uncertainty will be reported by the 95% confidence interval and the probability of acceptance curve. The confidence interval will be calculated using the non-parametric bootstrapping method (1,000 replicates re-sampled in randomized pairs with replacement from intervention and control groups). The cost-utility acceptability curve will be plotted (Fenwick & Byford, 2005; Willan, 2001). This curve shows the

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probability that the program is cost-effective in comparison with the alternative of usual care alone for different levels of investment to achieve an additional QALY. The "investment ceiling or frontier" is the maximum societal willingness to pay for this additional QALY. For the Spanish health system, the current year adjusted investment frontier will be set at conservative €40,000/QALY (40,000 to 50,000 E/QALY is normally used).

Additionally, sensitivity analysis will explore the robustness of the estimates and to determine the grade of dependence of the results in different scenarios. The first analysis will explore the influence of the participation rate in the intervention, as this could influence productivity by affecting the number of participants per unit of time provided by the personal trainer. The number of participants attended simultaneously because the 5G technology is approaching and multiple simultaneous connections could be provided in the future. A further simulation will evaluate variations due to the salary changes of the personal trainer, since these variations represent the major source of variability in economic studies (Sevick et al., 2000). The sunk costs (computer and Internet provider fee that new generation could already have) will be discounted in other sensitivity analysis. Finally, to sum-up, the robustness of cost-utility will be assessed by analyzing scenarios combining the influence of variations in staff salary, rate of participation, distance to the participant's home, and effectiveness, ranging from the lowest to the highest limit of the 95% confidence interval.

DISCUSSION

Providing care to relatives with dementia is an unforeseen duty that represents a continuous challenge for primary caregivers, as it involves great efforts and a personal commitment, and the majority of them have limited experience or training to provide care appropriately. Consequently, the role of caregiver may negatively impact on the physical, psychological, social, and financial well-being of caregivers (Bauer et al., 2012; Chiao et al., 2015; Erol et al., 2015; L. Fredman, Bertrand, R., Martire, L., Hochberg, M., Harris, E., 2006). In this sense, previous research has reported that caregivers are prone to experience a series of psychological symptoms, such as anxiety, depression, subjective burden, as well as physical impairments and lower levels of fitness in a greater extent than non-caregivers (Birkenhäger-Gillesse et al., 2018; Chiao et al., 2015; Delgado et al., 2014; Madruga, Gozalo, Prieto, Adsuar, & Gusi, 2020; Pérez-Fuentes et al., 2017; Salazar et al., 2016). As a consequence, all these negative effects significantly decrease the health-related quality of life of primary caregivers of relatives with dementia (Dawood, 2016; Del Rio Lozano et al., 2017; Flores et al., 2014; Garzón-Maldonado et al., 2016).

The increasing number of primary caregivers of relatives with dementia (Alzheimer's Disease International, 2016; Parra-Vidales, Soto-Pérez, Perez-Bartolomé, Franco-Martín, & Muñoz-Sánchez, 2017; Vandepitte et al., 2016) makes it necessary to provide these caregivers with, personalized interventions aimed at improving both physical and mental health, and thus quality of life of primary caregivers. Therefore, this type of interventions should be promoted.

The present protocol may serve as the basis for such an intervention. Indeed, the aim of the present study is to provide the primary caregivers of relatives with dementia with a physical exercise-based program that is focused on improving the health-related quality of life of these caregivers. Moreover, this intervention is an effort to overcome the constraints that the caregivers usually have to face when it comes to participating in a physical exercise program. These constraints usually are: absence of leisure-time, great distances to the sport facilities or financial problems (Blom, Zarit, Groot Zwaaftink, Cuijpers, & Pot, 2015; Chan et al., 2016). In addition, and, in accordance with previous recommendations (Domingues et al., 2018; Lamotte et al., 2017; Pot, Blom, & Willemse, 2015), the intervention will be personalized and Internet-based. In this way, we expect higher rates of adherence to the program. In particular, the physical exercise sessions will be delivered by means of an interactive web-based program while the caregiver will stay at home, and the personal trainer will be at the physical education laboratory. As our previously referenced protocol (Madruga, Prieto, et al., 2020), both the intensity and the types of the physical exercises will be adapted to each caregiver's fitness level and the space available

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at her home. The weekly schedule will also be agreed in accordance with the participant's availability and preference. For all mentioned above, the methodology of this study might be appropriate and robust to analyze the effects of the intervention on the targeted caregivers. Moreover, in order to eliminate potential limitations regarding the use of the Internet or its application (Ploeg et al., 2017) and/or difficulties with Internet browsing (Godwin, Mills, Anderson, & Kunik, 2013), caregivers will join a 1-hour session of training about uses of the Internet at caregivers' home prior to starting the intervention. The personal trainer will explain the procedure to login, to run the software and to logout the Internet session. Additionally, the personal trainer will phone the caregiver before each session commences to verify, whether the caregiver needs to start the application. Previous research has found that caregivers tend to show remarkable acceptance and a positive attitude towards this type of interventions (Mahmood et al., 2019).

On the other hand, and, in accordance with previous research findings, Internet-based interventions have shown to be effective and beneficial to improve physical and mental health, and thus the health-related (Hopwood et al., 2018; Ploeg et al., 2017; Sherifali et al., 2018). The use of a RCT approach in this study will additionally provide scientific evidences on the efficacy and cost-effectiveness of an Internet-based physical exercise intervention aimed at the targeted population. In addition, the outcomes of the present study might help policymakers promote Internet-based health support services that might contribute to lessen the investments of financial resources in hospitalizations, consultations, socio-sanitary services and the intake of medication.

Regarding the cost-effectiveness-related analysis of the physical exercise intervention, the most widely used method is to evaluate the outcomes in terms of the so-called quality-adjusted life years (QALYs) gained, because it can straddle gains in quantity of life as well as gains in quality of life in the same single metric using time-trade-offs (Torrance, 1997). According to this, we selected the EQ-5D-3L as a well-known tool for calculating the cost-utility of the intervention. In accordance with previous research, the use of standardized methods to assess physical and mental health as well as health-related quality of life among caregivers will provide more accurate outcomes, thus improving the effectiveness of the intervention. In this sense, we expect a series of positive outcomes in the caregivers subjected to the intervention, such as an improvement in physical fitness-related variables, as well as a decrease in subjective burden and psychological symptoms, such as anxiety, and depression (Marziali & Garcia, 2011; Stjernsward & Hansson, 2018).

If the study confirms the effectiveness of this intervention for primary caregivers of relatives with dementia, the research might be extended to caregivers of relatives with other diseases, such as stroke, cancer and Parkinson's or to caregivers who do not live together with the care-recipient, such as home-nursing caregivers or friends.

In addition, the step-by-step digital technology advances, such as 5G is advantageous because it could provide feasible simultaneous connections in rural areas, so that more caregivers could attend the intervention and basic literacy of new caregivers could reduce costs and increase the social interaction to enhance the value of the present research in the close future indeed.

Finally, the present study protocol shows some limitations that should be mentioned. First, the sample size is not very large, which reduces the potential to analyze subgroups. However, the estimation of the sample size has been appropriate to this RCT approach at evaluating the effectiveness and cost-utility of the program. Second, the generalization to other healthcare systems should be cautious because the healthcare system could differ among countries.

CONCLUSIONS

The intervention described in this protocol may be a feasible personalized way to help primary caregivers cope with the physical and psychological ailments caused by their caregiving-related responsibilities. Moreover, the generation of positive outcomes may also strengthen regional and national health policymakers to improve Internet-based care services, thus, lessen care-recipients' demands on health-care services. Finally, future research efforts should be done to elucidate, whether the present study might also have a positive impact on caregivers of people with other diseases.

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ANNEX

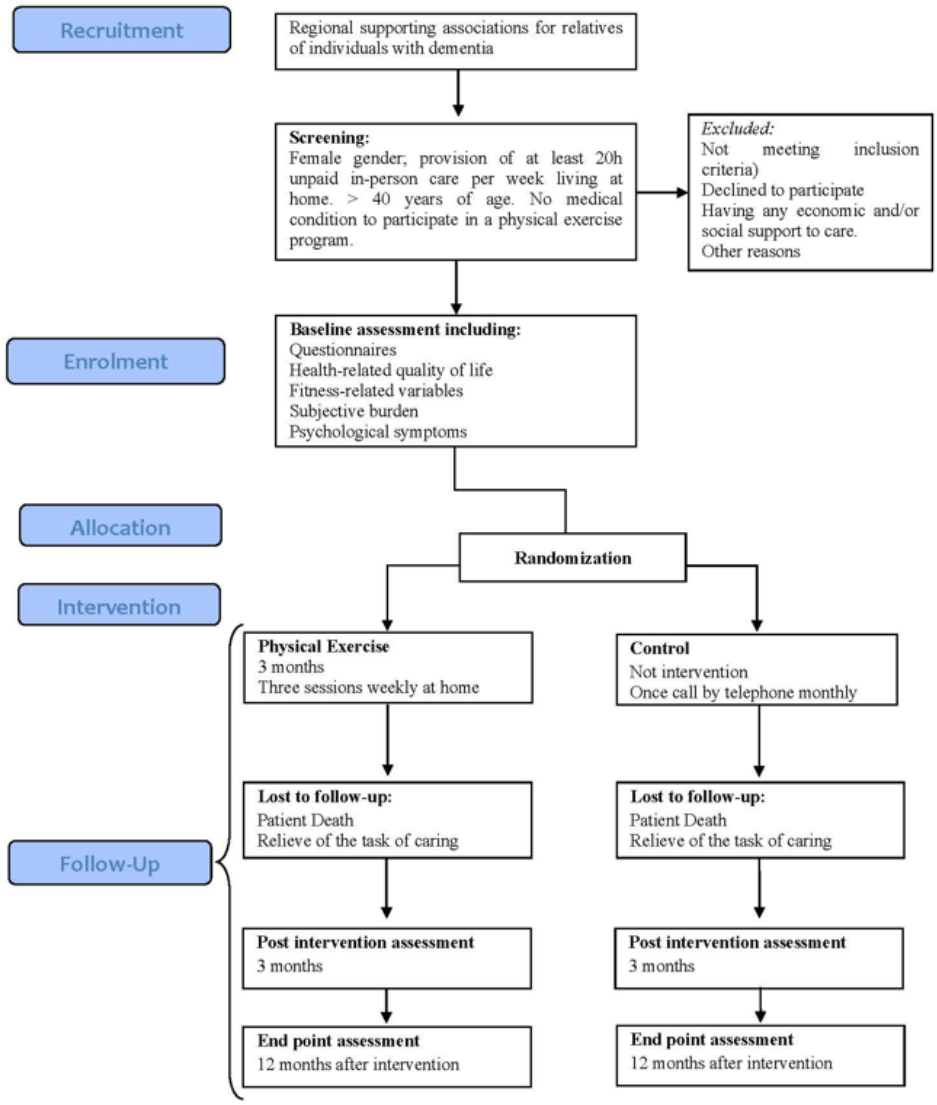

Figure 1: Flow chart of participants

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