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Testing the effectivity of the mixed virtual reality training Into D'mentia for informal caregivers of people with dementia: protocol for a longitudinal, quasi-experimental study.

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Keywords: dementia, informal caregivers, simulator, caregiver burden, empathy

ABSTRACT

Introduction: Informal caregivers (ICs) often feel (over)burdened by the care for a loved one with dementia and this can have various deleterious effects on both ICs and patients. Support for ICs is urgently needed and for this reason a dementia simulator (Into D'mentia) was developed in which ICs experience what it is like to have dementia. The simulator attempts to heighten ICs empathy and understanding for the patient and, in turn, diminish their own caregiver burden. The current study evaluates whether the simulator is effective on a number of outcomes.

Methods and analysis: A longitudinal, quasi-experimental study is ongoing in the Netherlands. We aim to recruit 142 ICs in total divided over 2 groups: 71 ICs in the intervention group and 71 ICs in the first control group. All participants will complete interviews and questionnaires at 4 time points; at baseline, 1 week, 2.5 and 15 months after the training. A second control group (not caregivers) is/will be tested at baseline in order to assess how ICs differ from the normal population on the variables of interest. The primary outcomes include: caregiver burden, empathy, caregiver sense of competence, social reliance, anxiety, depression and ICs subjective and objective health.

Ethics and dissemination: This study is being carried out in agreement with the Declaration of Helsinki and the protocol has been approved by the local ethics committees.

Registration details: This study is registered with The Netherlands National Trial Register (number = 5856).

Keywords: dementia, informal caregivers, simulator, caregiver burden, empathy

Strengths and limitations of the study

Strengths

- It is a longitudinal, prospective design with multiple assessments. This is a useful addition to the existing effect studies into interventions for ICs, which usually apply pre-post designs which makes it impossible to know if these interventions work in the longer term.
- We include both quantitative (questionnaires) and qualitative (semi-structured interviews) measurements.
- Control groups are included which was not always the case in previous intervention studies with ICs. Control group 1 makes it possible to attribute the findings to the intervention, instead of to other variables such as elapsed time. The non-ICs control group is used as a reference group at baseline, enabling us to characterize ICs more clearly as a group.

Limitations

- A potential limitation is that due to practical reasons the participants were not randomized. The simulator was available for free for 5 weeks only, in which it was impossible to recruit 141 informal caregivers. Instead, the groups are recruited consecutively and we aim to statistically control for differing variables using covariates.

BACKGROUND

The number of people living with dementia worldwide is currently estimated at 35.6 million. This number will double by 2030 and more than triple by 2050[1]. In the Netherlands 260,000 people were diagnosed with dementia in 2014. 70% of these people live at home and are dependent on informal caregivers (ICs) for their daily care[2]. ICs are mostly unpaid spouses, sons, daughters, friends or relatives.

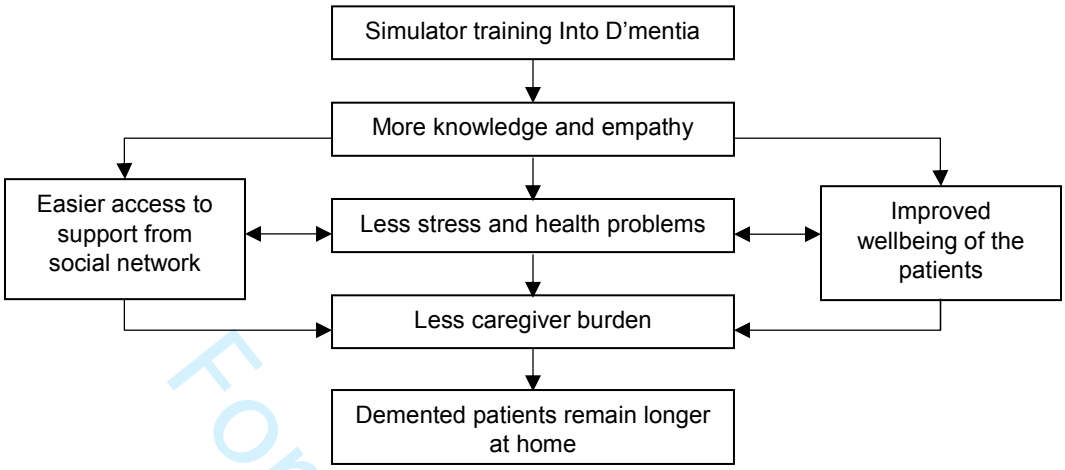
Although caregiving is satisfying for some ICs[3-5], it can also be very burdensome[6, 7]. ICs often experience higher rates of depression[8], poorer physical and mental health[9-11], a lower sense of well-being, more social isolation[12] and more financial burden[13] than people who do not provide care. The likelihood of nursing home admission for the person with dementia rises when their IC becomes overburdened and can no longer cope[14]. An intervention which supports ICs in their caregiving role is therefore very desirable.

In the past 10-15 years, several interventions have been developed to support ICs. These include: training and education programs, support groups, counseling, web-based and multi-component interventions. These have been found to be moderately effective in improving the quality of care and competence of caregivers[15-17], diminishing caregiver burden[17, 18], health related problems [19, 20], stress[20, 21], improving the quality of life of both ICs and their patients[22] and diminishing the dependency on professionals[17, 20]. However, most of these interventions lack practical tips and advice on how to apply the knowledge gained in daily life. The idea came to us that if ICs could actually experience symptoms of dementia themselves they might understand their patients better and in turn have more empathy for them. With this hypothesis in mind the mixed virtual reality simulator 'Into D'mentia' was developed in 2010[23]. We also included education and the use of support groups in our training (these take place after the ICs experience in the simulator) because these have been found to be beneficial in other interventions[24, 25].

The simulator's goal is to increase ICs knowledge and empathy for the person with dementia. It is hypothesized that this will lead to decreased stress levels, caregiver burden and health problems associated with caregiving in the ICs themselves, and that this in turn will lead to the person with dementia living at home for longer before being institutionalized (see Figure 1). A better understanding of dementia has been found to promote the wellbeing of ICs in a previous study[26]. In another study, when ICs cared in a more empathetic way for the person with dementia, their own stress level was reduced[27]. Professionals who have more (versus those who have less) empathy have also been found to have fewer burn-outs and are more satisfied with their work, while the people with dementia under their care adhere better to therapy and have better health related outcomes[27, 28].

The aim of the current study is to assess the effectivity of the Into D'mentia simulator on a number of variables over time including: empathy, caregiver burden, feelings of competence of caregiving, depression and anxiety, the relationship between ICs and their patients, and the health of ICs. Here we describe the design and protocol of this study.

Figure 1. The simulator's goals.



METHODS AND ANALYSIS

Design

A longitudinal, quasi-experimental study with 3 groups is ongoing. The study began in 2014, the final measurements will be made in 2017. Participants are evaluated 4 times: 1 week before the Into D'mentia training (T1), and 1 week, 2.5 weeks and 15 months after the training (T2, T3, T4 respectively). Control group 1 is tested at the same time intervals, starting at T1. Control group 2 is tested once, for baseline comparisons.

Study population

3 groups are created and consecutively recruited:

- The intervention group. This group receives the Into D'mentia simulator training.
  The group consists of informal caregivers of a relative, friend or spouse with dementia. The participants are recruited from de Wever in Tilburg, the Netherlands, an organization for eldercare; elderly federations; Alzheimer Nederland; case managers; centers for daytime activities for people with dementia and via social media.
  Inclusion criteria:
  - An informal caregiver for a spouse, family member, or friend with dementia; spend at least 8 hours a week caring for the patient who lives at home (not institutionalized).
  - At least 18 years old (no upper age limit).
  Exclusion criteria:
  - Physical disabilities which make entrance into the simulator impossible.
  - Severe communicative disabilities which make understanding of the simulator impossible (e.g. insufficient understanding of the Dutch language, blindness or deafness).
  - Self-reported severe psychological or medical disabilities which make the simulator too confusing (including self-reported dementia).
- Control group 1. This group also consists of ICs. The recruitment, inclusion and exclusion criteria are the same as for the intervention group. The only difference is that this group does not experience the simulator/intervention and as such is an attention-only group. This group is not

prohibited from usual care. After completion of the study, a group meeting will be organized as a reward for participating in the study. During this meeting, professionals will provide information about dementia and the participants will have the opportunity to ask questions.

- Control group 2. This group consists of people >18 years old, who do not care for a spouse, family member or friend with an illness or disability (including dementia). These participants are recruited by LJ and student-assistants, from both private and professional networks.

Procedure

Eligible participants receive oral and written information about the study from case managers, nurses, and supervisors at day-time activity centers; or only written information on social media. Eligible participants are invited to contact the researchers (LJ) by phone or e-mail if they have questions and to receive more information about the study. If they are interested in participating, the appointment for the first interview is scheduled and the questionnaires are sent. For the intervention group, an appointment for the intervention training is made at the same time. Written consent is also obtained. For the follow-up assessments (T2 – T4), participants are informed by letter, telephone or e-mail and invited to participate after which an appointment is scheduled.

For both the intervention and control group 1, 4 measurements take place; for all 4 assessments a semi-structured interview is conducted and a questionnaire booklet is provided. The interviews are administered in a standardized way by trained neuropsychologists and take place either at the participant's home or at Tilburg University depending on the ICs preference. The questionnaire booklet is sent to the participants before the appointment for the interview with the request that they complete it at home and bring it with them to the interview when they can receive help should any problems arise. Control group 2 is tested once, for baseline comparisons.

The questionnaires and interviews are identical for the 3 groups. The only exception being for control group 2, where questions about the person with dementia, the Caregiver Reaction Assessment Dutch (CRA-D) and the Short Sense of Competence Questionnaire (SSCQ) are not relevant and are therefore omitted for this group.

Intervention

The intervention is a mixed-reality dementia simulator training. The training consists of 3 parts: the simulation, an individual conversation with the trainer immediately after the simulation and a group meeting with the other participants 1-2 weeks later. In the simulator, the participants experience what it is like to have dementia. The training was developed based on literature reviews and on talks with caregivers, professionals and a number of people with dementia[23]. The caregivers, professionals and people with dementia were also involved in the process of developing, altering, and improving the intervention. They all approved of the final simulator, which we are currently using in this study. The simulator training takes place in a portable unit in which a little front yard, a bathroom and a kitchen are built. After a short, individual introduction, the participant enters the simulator unit. The participant wears a speaker vest, with microphones from which their ''inner voice'' tells the story. This inner voice gives them specific instructions, for example to turn on the radio which then appears to not work properly. The participant's ''daughter'' is projected on a screen and she behaves like many ICs do, for example talking about the patient while the patient is in the room, getting frustrated et cetera. Several audiovisual elements make the simulator interactive, allowing the participant to make choices and

thereby influence the storyline. After the simulation, each participant individually discusses their experiences and impressions in the simulator with the trainer. A group meeting with 8-12 other participants is organized 1-2 weeks after the training in order to help them to better understand and to implement their experiences and new knowledge into their daily lives. During this group meeting, experiences in the simulator are described in more detail and are put into perspective. In addition, professionals give information about dementia and some practical tips are shared. At the same time, the ICs can learn from each other's experiences.

Measures

Tables 1 and 2 give an overview of the variables assessed and instruments used at each time point. Short questionnaires (or self-made questions) were specifically chosen in order to reduce the time (about 45 minutes in total) required to complete, because ICs are typically busy and 82% overburdened[29]. The interviews take about 45 minutes to complete, leading to a time-investment of approximately 90 minutes per measurement per IC.

Outcomes

Primary outcomes

The primary outcomes chosen to assess how effective the Into D'mentia simulator are as follows: empathy, caregiver burden, depression and anxiety, the quality of the relationship between IC and patient, and caregiver's sense of competence.

- To measure empathy, the Interpersonal Reactivity Index (IRI)[30] is used. The IRI asks subjects to rate 28 items on several empathy-related statements on a 5-point Likert scale ranging from 'does not describe me well' to 'describes we very well'. The 28 items are clustered into 4 subscales, each made up of 7 different items: perspective taking, fantasy, empathic concern, and personal distress, leading to a multidimensional approach to empathy. The Cronbach's alpha for the subscales ranges from .70 to .76[31].
- Caregiver burden is evaluated by the Caregiver Reaction Assessment Dutch (CRA-D)[32]. The CRA-D measures both negative and positive reactions to caregiving. The questionnaire consists of 24 items, clustered into 5 dimensions: the impact of caregiving on disrupted schedule, financial problems, lack of family support, health problems, and the impact of caregiving on caregiver's self-esteem, with Cronbach's alpha ranging from .62 to .83[33]. The subjects report to what extent he or she agrees with the 24 statements on a 5-point scale.
- Anxiety and depression are measured using the Hospital Anxiety and Depression Scale (HADS)[34]. The HADS comprises 7 questions for anxiety and 7 questions for depression and takes 2 to 5 minutes to complete. The items are rated on a 4-point scale (0-3) and concern anxiety and depression symptoms from the last week. The scores on the subscales are added up and a cut-off score of 8 is used to indicate depressive or anxiety complaints. For the anxiety subscale, Cronbach's alpha ranges from .76 to .93, for the depression subscale it ranges from .72 to .90 in different studies[35].
- The quality of the relationship between IC and patient is evaluated using 2 questionnaires. The first is the Relationship Quality Index (RQI), which consists of 5 questions which can be answered on a 7-point Likert scale. The maximum score is 35. A higher score indicates a higher quality relationship[36].

The second questionnaire to measure relationship quality is based on the Affectual Solidarity (AS) questionnaire used for the Longitudinal Study of Generations (LSOG)[37], which in this study is named Quality of Relationship (QoR). This questionnaire evaluates 2 domains: Current relationship quality (QoR-current) (6 items), and Change in relationship quality (QoR-change) (5 items). The 6 items of the

QoR-current are evaluated on a 4-point scale. Scores range from 6 to 24, with a higher score indicating a better relationship quality. The 5 items of the QoR-change are statements regarding how much things have changed since the dementia diagnosis of a loved one. The statements are evaluated in a 5-point scale, range from 5 to 25, with a higher score indicating a lower relationship quality.

- Caregiver's sense of competence is assessed by the Short Sense of Competence Questionnaire (SSCQ), which consists of 7 items, rated according to a 5-point Likert scale (1-5). The items are clustered into 3 domains: Lack of satisfaction with the person with dementia as a recipient of care; Lack of satisfaction with one's own performance as a carer; and Consequences of involvement in care for the personal life of the carer. The total score ranges from 0 to 35, with a Cronbach's alpha of .76[38].

Secondary outcomes

Secondary outcomes include for the ICs: social reliance (use of social networks and participation) subjective and objective health, life events, quality of life and quality of sleep. The living situation of the person with dementia will also be assessed.

- Social reliance is measured by the Dutch version of the Inventory for Social Reliance. The questionnaire evaluates both the quantitative and qualitative aspects of social support. The quantitative part consists of 2 items; the number of good friends and the number of acquaintances in the participants' neighborhood. The qualitative part entails 11 items; rated according to a 4-point Likert scale, which cover 3 aspects of social support: perceived emotional support, actual emotional support, mutual visiting and 1 rest item[39, 40].
- Subjective health is evaluated by asking the ICs if they had cognitive, depressive or anxiety complaints in the last 4 weeks. Objective health in the ICs is assessed using the following (separate) measures: the number of medications the IC personally uses, the number of hospital admissions, visits to the general practitioner, and visits to the hospital in the last month.
- To assess life events, the participants answer the following self-made written question concerning the presence and impact of a positive or negative life event 'In the past month, did something happen in your life which had a major impact on you? This may be something either pleasant or sad'. The subjects can choose between 'no' or 'yes, namely.. '. If the answer is yes, the next question is what the total impact of the experience is, which the subject can rate according to a 5-point Likert scale ranging from 'very negative impact' to 'very positive impact'.
- Quality of life and quality of sleep are both evaluated using 1 self-made Likert scale. The subject is asked to rate their quality of sleep and quality of life at 'this' moment in their lives, by putting a cross on this line:

0 25 50 75 100
|_____|_____|_____|_____|
Very bad Very good

- The living situation of the person with dementia is assessed, by asking the ICs if the person still lives at home or if he or she has been institutionalized.

Table 1. Primary outcomes

	Variable/Instrument	T1	T2	T3	T4
Primary outcomes					
Empathy	Interpersonal Reactivity Index[30]	X	X	X	X
Caregiver burden	Caregiver Reaction Assessment - Dutch*[32]	X	X	X	X

Depressive complaints	Hospital Anxiety and Depression Scale – subscale depression[34]	X	X	X	X
Anxiety complaints	Hospital Anxiety and Depression Scale – subscale anxiety[34]	X	X	X	X
Quality of the relationship	Relationship Quality Index[36]	X	X	X	X
	Quality of Relationship[37]	X	X	X	X
Caregiving competence	Short Sense of Competence Questionnaire*[38]	X	X	X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3. *: Question for the intervention group and control group 1 only.

Table 2. Secondary outcomes

	Variable/Instrument		T1	T2	T3	T4
Social reliance	Inventory for Social Reliance[39]		X	X	X	X
Subjective health	Cognitive complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience cognitive complaints?'*	X			
		Self-made item: 'In the previous month, have you experienced cognitive complaints?'	X	X	X	X
	Depressive complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience depressive complaints?'*	X			
		Self-made item: 'In the previous month, have you experienced depressive complaints?'	X	X	X	X
	Anxiety complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience anxiety complaints?'*	X			
		Self-made item: 'In the previous month, have you experienced anxiety complaints?'	X	X	X	X
Objective health	Number of hospital admissions		X	X	X	X
	Number of hospital visits		X	X	X	X
	Number of GP visits		X	X	X	X
Life events	Self-made item concerning the presence and impact of a positive of negative life event: 'Last month, did something happen in your life which had a major impact on you? This may be something either pleasant or sad'		X	X	X	X
Quality of life	Self-made item concerning the quality of life of the ICs: 'How would you rate your quality of life on this point in your life?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good)		X	X	X	X
Quality of sleep	Self-made item about the quality of sleep: 'Before the dementia of your spouse/friend/relative, how would you have rated your quality of sleep?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good).*		X			
	Self-made item about the quality of sleep: 'How would you have rated your quality of sleep on this point in your life?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good).		X	X	X	X
Health and living situation patient	Self-made item concerning the progression of the dementia of the patient: 'How is he or she doing compared to the time of the last interview?' The possible answers are better, the same or worse, than the last interview.*			X	X	X
	Self-made item concerning the living situation of the patient: 'Has something changed in the living situation of the patient since the last interview?'*			X	X	X
	Self-made item about the concerns of the ICs about the dementia of the patient: 'Do you have any new concerns about the dementia since the last interview?'*			X	X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3. *: Question for the intervention group and control group 1 only.

Possible determinants

Depending on the specific outcome considered, the primary and secondary outcomes (as given above) are either dependent or independent variables. A wide range of possible determinants (factors in the prediction model and/or covariates) are additionally taken into account, based on what is currently known from the literature about ICs. These include: sociodemographic variables, medicine use of both ICs and the people with dementia they care for, and clinical variables regarding the dementia such as the type and time since diagnosis. Finally, a couple of qualitative variables are also assessed, e.g. subjective experiences with the simulator (intervention group). Table 3 lists the specific variables assessed and instruments used.

Table 3. Possible determinants

	Variable/Instrument	T1	T2	T3	T4
Sociodemographic and clinical variables of the ICs					
Age, gender, education, employment status		X			
Medicine use		X			
Presence and severity of physical disabilities	Self-made question: 'Do you have any physical disabilities and if so, to what extent do these interfere with caregiving*?'	X			
Presence and severity of psychological disabilities	Self-made question: 'Do you have any psychological disabilities and if so, to what extent do these interfere with caregiving*?'	X			
Variables concerning caregiving	Relationship with the patient with dementia (spouse/daughter/son/something else)*	X			
	Distance to the patient (shares household/walking distance/in the same city/in a different city)*	X			
	Days providing care a week*	X			
	Hours providing care a week*	X			
	Years since first time providing care for this patient*	X			
	Support of professionals (e.g. housekeeper, case-manager)	X			
	Perceived support of friends or family*	X			
Clinical variables of the patient with dementia*					
Diagnosis	Alzheimer's disease/Vascular dementia/Parkinson's Disease Dementia/Frontotemporal Dementia/other/unknown	X			
Time since diagnosis (in years)		X			
Medicine use		X			
Comorbidities	Physical comorbidities	X			
	Psychological comorbidities	X			
Support of professional (e.g. physiotherapist)		X			
Self-made items regarding the subjective effectivity of the training**					
'Does the simulator give an accurate reflection of what a demented person goes through?'			X	X	X
'Did the simulator meet your expectations?'			X	X	X
'Do you think the simulator is useful?'			X	X	X
'Did you feel supported by the experiences and stories of the other participants in the group meeting?'			X	X	X
'Did the group meeting meet your expectations?'			X	X	X
'Do you think the group meeting is useful?'			X	X	X
'Did the whole training (simulator and group meeting together) had a personal impact on you?'			X	X	X
'Do you think that the whole training helps you to be a more effective caregiver?'			X	X	X
'Do you think the whole training has helped you to understand your spouse/relative/friend?'			X	X	X
'Do you think that you are better prepared for what is going to happen in the future?'			X	X	X
'Are you surer of your qualities because of the training?'			X	X	X
'Did you learn anything from the training? And if yes, what?'			X	X	X
'Do you do anything different in caring because of the training? And if yes, what?			X	X	X
'Do you think the training missed anything? And if yes, what?'				X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3. *: Question for the intervention group and control group 1 only. **: Question for the intervention group only.

Planned statistical analyses

SPSS Statistics 22 will be used for the statistical analyses. Parametric and non-parametric tests will be used to determine if the 3 groups are comparable at baseline on 4 variables, 3 caregiver variables (gender, age and level of education) and 1 person with dementia variable (time since diagnosis). Variables that differ will be used as covariates in the subsequent analyses.

Cross-sectional analyses will be used to evaluate group differences at each of the individual time points (T2-T4) and include $\chi 2$ for categorical variables, the Mann-Whitney U test for ordinal data, and the Student t test or multivariate analysis of variance ((M)AN(C)OVA) for continuous dependent variables. Differences across the time points will be analyzed using multilevel analysis, which allows inclusion of all available data (i.e. also those from participants with missing data).

The predictive value of the determinants for the primary and secondary outcome measures at T2, T3, and T4 will be determined using multivariate regression analysis (2 time points) or multilevel analysis (> 2 time points). Potential predictors are defined as variables with at least a marginally significant association ($p < .10$) with the outcome. Only these variables will be included in the subsequent analyses to determine the most important predictors. Effects with a 2-tailed $p < .05$ are considered statistically significant. Missing data will be imputed where possible.

A prediction model will be developed to define the most valuable variables for the effectivity of this intervention. Possible predictors are age, gender, relationship with the patient and hours of care.

The qualitative questions in the interviews will be analyzed using descriptive statistics and frequencies.

Sample size and power calculation

The sample size needed is calculated with G*Power, based on the main research question: does the simulator training increase the empathy of informal caregivers? Based on an alpha level of .05 and a power of .80, 64 participants per group are needed to be able to detect a medium difference ($d = 0.5$) between the groups. We expect about 10% drop-out during the 1-year follow-up period due to mortality of the ICs or the person the caregivers care for, or due to refusal to continue participation. Therefore, we aim to include at least 71 participants in each group; 3*71 = 213 participants in total.

ETHICS AND DISSEMINATION

Ethical considerations

This study is non-invasive and imposes no risk on either the participating ICs or the people with dementia. This protocol has been approved by the psychological ethical committees of both the Tilburg School of Social and Behavioral Sciences, Tilburg University and De Wever (a care organisation for eldercare) in Tilburg, the Netherlands. Written informed consent is obtained from all participants, in accordance with the 'Helsinki Declaration' (Seoul Revision, 2008). The data is stored anonymously and only the primary researchers (LJ, RM, and MM) have access to the data. This study has been registered by The Dutch National Trial Register (NTR), number (TC): 5856.

Dissemination

The results obtained will be disseminated to the scientific and general public by publication in national and international (peer-reviewed) scientific and professional journals, as well as by presentations at conferences and meetings with professionals dealing with (informal caregivers of people with) dementia. The data will not be made public, assuring the study participants' privacy. Requests for data sharing will be considered on an individual basis, for appropriate research purposes only.

DISCUSSION

This is the first study in which the effectivity of a mixed virtual reality dementia simulator is extensively tested in ICs in a controlled trial. While multiple interventions for ICs have been designed and tested[41], this is the first dementia simulator in which ICs actually experience what it is like to have dementia, not only on a functional level, but also emotionally and socially. The focus on experience-based learning makes this intervention very practical.

Strong elements of this study are its longitudinal prospective design with multiple assessments. This is a useful addition to the existing effect studies into interventions for ICs, which usually apply pre-post designs which makes it impossible to know if these interventions work in the longer term. In addition, we include both quantitative (questionnaires) and qualitative (semi-structured interviews) measurements. Also, control groups are included which was not always the case in previous intervention studies with ICs. Control group 1 makes it possible to attribute the findings to the intervention, instead of to other variables such as elapsed time. The non-ICs control group is used as a reference group at baseline, enabling us to characterize ICs more clearly as a group.

In conclusion, we hope that this study will determine how effective (or not) the Into D'mentia training is on a variety of variables including empathy and caregiver burden. Furthermore, we believe that it has the potential to contribute to existing knowledge about ICs. The dementia simulator is expected to be specifically effective in enhancing the quality of life of both caregivers and the people with dementia they care for by helping ICs understand dementia better in a more personal way.

More informal caregivers than ever before are involved in the care for a family member or friend living with dementia. Helping them in their task should be a priority in health care services around the world. At the moment the Into D'mentia training is too expensive for many individual ICs (the training costs €240,- per person). If it proves to be effective (on one or more outcomes) the next step would be to get it implemented into standard care, making it available for all ICs and also for care professionals. The ultimate goal is to assist ICs in the best possible way in their task of caring for their loved ones with dementia, a task most come unprepared to and a task that no one asks for.

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Contributors
LHJ, REM, BWJMJ, JR, RMD, and MMS contributed to study concept, planning and data acquisition, LJ, REM and MMS will contribute to the statistical analyses, publication and dissemination of findings. LHJ wrote the first manuscript, all other authors provided critical feedback during the manuscript development and approved of the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing Interests
The authors declare that they have no competing interests

Ethics approval
Approval for this study was provided by the psychological ethical committees of both the Tilburg School of Social and Behavioral Sciences, Tilburg University (number EC-2015.25) and De Wever (a care organisation for eldercare) in Tilburg, the Netherlands. Written consent is obtained from all participants.

Data sharing statement
Data are sensitive and the first priority in sharing data will be protection of study participants' privacy. Therefore, this will not be a public use dataset. The authors will consider requests for data sharing on an individual basis, for appropriate research purposes, after publication of the major findings of the study.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	-1 (title page)	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	3	
Methods				
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-9	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	10	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-9	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10	
Bias	9	Describe any efforts to address potential sources of bias	10	
Study size	10	Explain how the study size was arrived at	10	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Testing the effectivity of the mixed virtual reality training Into D'mentia for informal caregivers of people with dementia: protocol for a longitudinal, quasi-experimental study.

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Testing the effectivity of the mixed virtual reality training Into D'mentia for informal caregivers of people with dementia: protocol for a longitudinal, quasi-experimental study.

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ABSTRACT

Introduction: Informal caregivers for people with dementia (hereafter: caregivers) often feel (over)burdened by the care for a loved one with dementia and this can have various deleterious effects on both caregivers and patients. Support for caregivers is urgently needed and for this reason a dementia simulator (Into D'mentia) was developed in which caregivers experience what it is like to have dementia. The simulator attempts to heighten caregivers' empathy and understanding for the patient and, in turn, diminish their own caregiver burden. The current study evaluates whether the simulator is effective on a number of outcomes.

Methods and analysis: A longitudinal, quasi-experimental study is ongoing in the Netherlands. We aim to recruit 142 caregivers in total divided over 2 groups: 71 caregivers in the intervention group and 71 caregivers in the control group. All participants will complete interviews and questionnaires at 4 time points; at baseline, 1 week, 2.5 months and 15 months after the training. The primary outcomes include: empathy, caregiver burden, caregiver sense of competence, social reliance, anxiety, depression and caregivers' subjective and objective health.

Ethics and dissemination: This study is being carried out in agreement with the Declaration of Helsinki and the protocol has been approved by the local ethics committees.

Registration details: This study is registered with The Netherlands National Trial Register (number = NTR5856).

Keywords: dementia, informal caregiver, virtual reality, caregiver burden, empathy

Strengths and limitations of the study

Strengths

- It is a longitudinal, prospective design with multiple assessments. This is a useful addition to the existing effect studies into interventions for caregivers, which usually apply pre-post designs making it impossible to know if these interventions work in the longer term.
- We include both quantitative (questionnaires) and qualitative (semi-structured interviews) measurements.
- A control group is included which was not always the case in previous intervention studies with caregivers. The control group makes it possible to attribute the findings to the intervention, instead of to other variables such as elapsed time.

Limitations

- A potential limitation is that due to practical reasons the participants were not randomized. The simulator was available for free for 5 weeks only, in which we deemed it impossible to recruit enough caregivers for both the intervention and control group. Instead, the groups are recruited consecutively and we aim to statistically control for differing variables using covariates.

BACKGROUND

The number of people living with dementia worldwide is currently estimated at 35.6 million. This number will double by 2030 and more than triple by 2050[1]. In the Netherlands 260,000 people were diagnosed with dementia in 2014. 70% of these people live at home and are dependent on informal caregivers (hereafter: caregivers) for their daily care[2]. Caregivers are mostly unpaid spouses, sons, daughters, friends or relatives.

Although caregiving is satisfying for some caregivers[3-5], it can also be very burdensome[6, 7]. Caregivers often experience higher rates of depression[8], poorer physical and mental health[9-11], a lower sense of well-being, more social isolation[12] and more financial burden[13] than people who do not provide care. The likelihood of nursing home admission for the person with dementia rises when their caregiver becomes overburdened and can no longer cope[14]. An intervention which supports caregivers in their caregiving role is therefore very desirable.

In the past 10-15 years, several interventions have been developed to support caregivers. These include: training and education programs, support groups, counseling, web-based and multi-component interventions. These have been found to be moderately effective in improving the quality of care and competence of caregivers[15-17], diminishing caregiver burden[17, 18], health related problems [19, 20], stress[20, 21], improving the quality of life of both caregivers and their patients[22] and diminishing the dependency on professionals[17, 20]. However, most of these interventions lack practical tips and advice on how to apply the knowledge gained in daily life. The idea came to us that if caregivers could actually experience symptoms of dementia themselves they might understand their patients better and in turn have more empathy for them. With this hypothesis in mind the mixed virtual reality simulator 'Into D'mentia' was developed in 2010[23]. We also included education and the use of support groups in our training (these take place after the caregivers experience in the simulator) because these have been found to be beneficial in other interventions[24, 25].

The simulator's goal is to increase caregivers knowledge and empathy for the person with dementia. It is hypothesized that this will lead to decreased stress levels, caregiver burden and health problems associated with caregiving in the caregivers themselves, and that this in turn will lead to the person with dementia living at home for longer before being institutionalized (see Figure 1). A better understanding of dementia has been found to promote the wellbeing of caregivers in a previous study[26]. In another study, when caregivers cared in a more empathetic way for the person with dementia, their own stress level was reduced[27]. Professionals who have more (versus those who have less) empathy have also been found to have fewer burn-outs and are more satisfied with their work as a professional caregiver, while the people with dementia under their care adhere better to therapy and have better health related outcomes[27, 28].

The aim of the current study is to assess the effectivity of the Into D'mentia simulator on a number of variables over time including: empathy, caregiver burden, feelings of competence of caregiving, depression and anxiety, the relationship between caregivers and their patients, and caregivers' health. This will be the first study that evaluates an intervention which attempts to simulate dementia. Here we describe the design and protocol of this study.

METHODS AND ANALYSES

Design

A longitudinal, quasi-experimental study with 2 groups is ongoing. The study began in 2014, the final measurements will be made in 2017. Participants are evaluated 4 times: 1 week before the Into D'mentia training (T1), and 1 week, 2.5 months and 15 months after the training (T2, T3, T4 respectively). The control group is tested at the same time intervals, starting at T1. Figure 2 shows a graph of the time schedule.

Study population

2 groups are created and consecutively recruited:

- The intervention group. This group receives the Into D'mentia simulator training (and is not prohibited from usual care).
  The group consists of informal caregivers of a relative, friend or spouse with dementia. The participants are recruited from de Wever in Tilburg, the Netherlands, an organization for eldercare; elderly federations; Alzheimer Nederland; case managers; centers for daytime activities for people with dementia and via social media.
  Inclusion criteria:
  - An informal caregiver for a spouse, family member, or friend with dementia; spend at least 8 hours a week caring for the patient who lives at home (not institutionalized).
  - At least 18 years old (no upper age limit).
  Exclusion criteria:
  - Physical disabilities which make entrance into the simulator impossible.
  - Severe communicative disabilities which make understanding of the simulator impossible (e.g. insufficient understanding of the Dutch language, blindness or deafness).
  - Self-reported severe psychological or medical disabilities which make the simulator too confusing (including self-reported dementia).
- The control group. This group also consists of caregivers. The recruitment, inclusion and exclusion criteria are the same as for the intervention group. The only difference is that this group does not experience the simulator/intervention and as such is an attention-only group. This group is not prohibited from usual care. After completion of the study, a group meeting will be organized as a reward for participating in the study. During this meeting, professionals will provide information about dementia and the participants will have the opportunity to ask questions.

Procedure

Eligible participants receive oral and written information about the study from case managers, nurses, and supervisors at day-time activity centers; or only written information on social media. Eligible participants are invited to contact the researchers (LJ) by phone or e-mail if they have questions and to receive more information about the study. If they are interested in participating, the appointment for the first interview is scheduled and the questionnaires are sent. For the intervention group, an appointment for the intervention training is made at the same time. Written consent is also obtained. For the follow-up assessments (T2 – T4), participants are informed by letter, telephone or e-mail and invited to participate after which an appointment is scheduled.

For both the intervention and the control group, 4 measurements take place; for all 4 assessments a semi-structured interview is conducted and a questionnaire booklet is provided. The interviews are administered in a standardized way by trained neuropsychologists and take place either at the participant's home or at Tilburg University depending on the caregivers' preference. The questionnaire booklet is sent to the participants before the appointment for the interview with the request that they complete it at home and bring it with them to the interview when they can receive help should any problems arise.

The questionnaires and interviews are identical for the 2 groups. The only exception being for the control group, where questions about the simulator training are not relevant and therefore omitted.

Intervention

The intervention is a mixed-reality dementia simulator training. The training consists of 3 parts: the simulation, an individual conversation with the trainer immediately after the simulation and a group meeting with the other participants 1-2 weeks later. In the simulator, the participants experience what it is like to have dementia. The training was developed based on literature reviews and on talks with caregivers, professionals and a number of people with dementia[23]. The caregivers, professionals and people with dementia were also involved in the process of developing, altering, and improving the intervention. They all approved of the final simulator, which we are currently using in this study. The simulator training takes place in a portable unit in which a little front yard, a bathroom and a kitchen are built. After a short, individual introduction, the participant enters the simulator unit. The participant wears a speaker vest, with microphones from which their ''inner voice'' tells the story. This inner voice gives them specific instructions, for example to turn on the radio which then appears to not work properly. The participant's ''daughter'' is projected on a screen using a beamer and she behaves like many caregivers do, for example talking about the patient while the patient is in the room, getting frustrated et cetera. Several audiovisual elements make the simulator interactive, allowing the participant to make choices and thereby influence the storyline. Empathic reactions of negative situations (like caring for a relative with pain, or in this case, dementia), can lead to stress, or negative changes in neural networks[29]. To ensure the safety and well-being of the participants, immediately after the training an individual conversation with the trainer is organized. During this conversation, the participants discuss their experiences in the simulator and the trainer comforts the participants if needed. If the participants are heavily distressed, they can also telephone the research team (all trained psychologists) for help. The participants are encouraged to discuss their experiences in the simulator with family members or friends regardless of immediate stress reactions. The participants can call the research team if they experience any negative reactions which cannot wait until the group meeting. A group meeting with 8-12 other participants is organized 1-2 weeks after the training in order to help them to better understand and to implement their experiences and new knowledge into their daily lives. During this group meeting, experiences in the simulator are described in more detail and are put into perspective. In addition, professionals give information about dementia and some practical tips are shared. At the same time, the caregivers can learn from each other's experiences.

Measures

Tables 1 and 2 give an overview of the variables assessed and instruments used at each time point. Short questionnaires (or self-made questions) were specifically chosen in order to reduce the time (about 45 minutes in total) required to complete, because caregivers are typically busy and 82%

overburdened[30]. The interviews take about 45 minutes to complete, leading to a time-investment of approximately 90 minutes per measurement per caregiver.

Outcomes

Primary outcomes

The primary outcomes chosen to assess how effective the Into D'mentia simulator are as follows: empathy, caregiver burden, depression and anxiety, the quality of the relationship between caregiver and patient, and caregiver's sense of competence.

- To measure empathy, the most important primary outcome, the Interpersonal Reactivity Index (IRI)[31] is used. The IRI asks subjects to rate 28 items on several empathy-related statements on a 5-point Likert scale ranging from 'does not describe me well' to 'describes me very well'. The 28 items are clustered into 4 subscales, each made up of 7 different items: perspective taking, fantasy, empathic concern, and personal distress, leading to a multidimensional approach to empathy. The Cronbach's alpha for the subscales ranges from .70 to .76[32].
- Caregiver burden is evaluated by the Caregiver Reaction Assessment Dutch (CRA-D)[33]. The CRA-D measures both negative and positive reactions to caregiving. The questionnaire consists of 24 items, clustered into 5 dimensions: the impact of caregiving on disrupted schedule, financial problems, lack of family support, health problems, and the impact of caregiving on caregiver's self-esteem, with Cronbach's alpha ranging from .62 to .83[34]. The subjects report to what extent he or she agrees with the 24 statements on a 5-point scale.
- Anxiety and depression are measured using the Hospital Anxiety and Depression Scale (HADS)[35]. The HADS comprises 7 questions for anxiety and 7 questions for depression and takes 2 to 5 minutes to complete. The items are rated on a 4-point scale (0-3) and concern anxiety and depression symptoms from the last week. The scores on the subscales are added up and a cut-off score of 8 is used to indicate depressive or anxiety complaints. For the anxiety subscale, Cronbach's alpha ranges from .76 to .93, for the depression subscale it ranges from .72 to .90 in different studies[36].
- The quality of the relationship between caregiver and patient is evaluated using 2 questionnaires. The first is the Relationship Quality Index (RQI), which consists of 5 questions which can be answered on a 7-point Likert scale. The maximum score is 35. A higher score indicates a higher quality relationship[37]. The second questionnaire to measure relationship quality is based on the Affectual Solidarity (AS) questionnaire used for the Longitudinal Study of Generations (LSOG)[38], which in this study is named Quality of Relationship (QoR). This questionnaire evaluates 2 domains: Current relationship quality (QoR-current) (6 items), and Change in relationship quality (QoR-change) (5 items). The 6 items of the QoR-current are evaluated on a 4-point scale. Scores range from 6 to 24, with a higher score indicating a better relationship quality. The 5 items of the QoR-change are statements regarding how much things have changed since the dementia diagnosis of a loved one. The statements are evaluated in a 5-point scale, range from 5 to 25, with a higher score indicating a lower relationship quality.
- Caregiver's sense of competence is assessed by the Short Sense of Competence Questionnaire (SSCQ), which consists of 7 items, rated according to a 5-point Likert scale (1-5). The items are clustered into 3 domains: Lack of satisfaction with the person with dementia as a recipient of care; Lack of satisfaction with one's own performance as a carer; and Consequences of involvement in care for the personal life of the carer. The total score ranges from 0 to 35, with a Cronbach's alpha of .76[39].

Secondary outcomes

Secondary outcomes include for the caregivers: social reliance (use of social networks and participation)

subjective and objective health, life events, quality of life and quality of sleep. The living situation of the person with dementia will also be assessed.

- Social reliance is measured by the Dutch version of the Inventory for Social Reliance. The questionnaire evaluates both the quantitative and qualitative aspects of social support. The quantitative part consists of 2 items; the number of good friends and the number of acquaintances in the participants' neighborhood. The qualitative part entails 11 items; rated according to a 4-point Likert scale, which cover 3 aspects of social support: perceived emotional support, actual emotional support, mutual visiting and 1 rest item[40, 41].
- Subjective health is evaluated by asking the caregivers if they had cognitive, depressive or anxiety complaints in the last 4 weeks. Objective health in the caregivers is assessed during the semi-structured interviews using the following (separate) measures (relying on self-report): the number of medications the caregiver personally uses, the number of hospital admissions, visits to the general practitioner, and visits to the hospital in the last month.
- To assess life events, the participants answer the following self-made written question concerning the presence and impact of a positive or negative life event 'In the past month, did something happen in your life which had a major impact on you? This may be something either pleasant or sad'. The subjects can choose between 'no' or 'yes, namely.. '. If the answer is yes, the next question is what the total impact of the experience is, which the subject can rate according to a 5-point Likert scale ranging from 'very negative impact' to 'very positive impact'.
- Quality of life and quality of sleep are both evaluated using 1 self-made Likert scale. The subject is asked to rate their quality of sleep and quality of life at 'this' moment in their lives, by putting a cross on this line:

0 25 50 75 100
|_____|_____|_____|_____|
Very bad Very good

- The living situation of the person with dementia is assessed, by asking the caregivers if the person still lives at home or if he or she has been institutionalized.

Table 1. Primary outcomes

	Variable/Instrument	T1	T2	T3	T4
Primary outcomes					
Empathy	Interpersonal Reactivity Index[31]	X	X	X	X
Caregiver burden	Caregiver Reaction Assessment - Dutch[33]	X	X	X	X
Depressive complaints	Hospital Anxiety and Depression Scale – subscale depression[35]	X	X	X	X
Anxiety complaints	Hospital Anxiety and Depression Scale – subscale anxiety[35]	X	X	X	X
Quality of the relationship	Relationship Quality Index[37]	X	X	X	X
	Quality of Relationship[38]	X	X	X	X
Caregiving competence	Short Sense of Competence Questionnaire[39]	X	X	X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3.

Table 2. Secondary outcomes

	Variable/Instrument		T1	T2	T3	T4
Social reliance	Inventory for Social Reliance[40]		X	X	X	X
Subjective	Cognitive	Self-made item: 'Before the dementia of your	X			

health	complaints	spouse/friend/relative, did you experience cognitive complaints?'				
		Self-made item: 'In the previous month, have you experienced cognitive complaints?'	X	X	X	X
	Depressive complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience depressive complaints?'	X			
		Self-made item: 'In the previous month, have you experienced depressive complaints?'	X	X	X	X
	Anxiety complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience anxiety complaints?'	X			
		Self-made item: 'In the previous month, have you experienced anxiety complaints?'	X	X	X	X
Objective health	Number of hospital admissions		X	X	X	X
	Number of hospital visits		X	X	X	X
	Number of GP visits		X	X	X	X
Life events	Self-made item concerning the presence and impact of a positive of negative life event: 'Last month, did something happen in your life which had a major impact on you? This may be something either pleasant or sad'		X	X	X	X
Quality of life	Self-made item concerning the quality of life of the caregivers: 'How would you rate your quality of life on this point in your life?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good)		X	X	X	X
Quality of sleep	Self-made item about the quality of sleep: 'Before the dementia of your spouse/friend/relative, how would you have rated your quality of sleep?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good).		X			
	Self-made item about the quality of sleep: 'How would you have rated your quality of sleep on this point in your life?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good).		X	X	X	X
Health and living situation patient	Self-made item concerning the progression of the dementia of the patient: 'How is he or she doing compared to the time of the last interview?' The possible answers are better, the same or worse, than the last interview.			X	X	X
	Self-made item concerning the living situation of the patient: 'Has something changed in the living situation of the patient since the last interview?'			X	X	X
	Self-made item about the concerns of the caregivers about the dementia of the patient: 'Do you have any new concerns about the dementia since the last interview?'			X	X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3.

Possible determinants

Depending on the specific outcome considered, the primary and secondary outcomes (as given above) are either dependent or independent variables. A wide range of possible determinants (factors in the prediction model and/or covariates) are additionally taken into account, based on what is currently known from the literature about caregivers. These include: sociodemographic variables, medicine use of both caregivers and the people with dementia they care for, and clinical variables regarding the dementia such as the type and time since diagnosis. These data rely on self-report of the informal caregiver. Finally, a couple of qualitative variables are also assessed, e.g. subjective experiences with the simulator (intervention group). Table 3 lists the specific variables assessed and instruments used.

Table 3. Possible determinants

Variable/Instrument	T1	T2	T3	T4
Sociodemographic and clinical variables of the caregivers				
Age, gender, education, employment status	X			
Medicine use	X			

Presence and severity of physical disabilities	Self-made question: 'Do you have any physical disabilities and if so, to what extent do these interfere with caregiving?'	X			
Presence and severity of psychological disabilities	Self-made question: 'Do you have any psychological disabilities and if so, to what extent do these interfere with caregiving?'	X			
Variables concerning caregiving	Relationship with the patient with dementia (spouse/daughter/son/something else)	X			
	Distance to the patient (shares household/walking distance/in the same city/in a different city)	X			
	Days providing care a week	X			
	Hours providing care a week	X			
	Years since first time providing care for this patient	X			
	Support of professionals (e.g. housekeeper, case-manager)	X			
	Perceived support of friends or family	X			
Clinical variables of the patient with dementia					
Diagnosis	Alzheimer's disease/Vascular dementia/Parkinson's Disease Dementia/Frontotemporal Dementia/other/unknown	X			
Time since diagnosis (in years)		X			
Medicine use		X			
Comorbidities	Physical comorbidities	X			
	Psychological comorbidities	X			
Support of professional (e.g. physiotherapist)		X			
Self-made items regarding the subjective effectivity of the training*					
'Does the simulator give an accurate reflection of what a demented person goes through?'			X	X	X
'Did the simulator meet your expectations?'			X	X	X
'Do you think the simulator is useful?'			X	X	X
'Did you feel supported by the experiences and stories of the other participants in the group meeting?'			X	X	X
'Did the group meeting meet your expectations?'			X	X	X
'Do you think the group meeting is useful?'			X	X	X
'Did the whole training (simulator and group meeting together) had a personal impact on you?'			X	X	X
'Do you think that the whole training helps you to be a more effective caregiver?'			X	X	X
'Do you think the whole training has helped you to understand your spouse/relative/friend?'			X	X	X
'Do you think that you are better prepared for what is going to happen in the future?'			X	X	X
'Are you surer of your qualities because of the training?'			X	X	X
'Did you learn anything from the training? And if yes, what?'			X	X	X
'Do you do anything different in caring because of the training? And if yes, what?			X	X	X
'Do you think the training missed anything? And if yes, what?'				X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3. *: Question for the intervention group only.

Planned statistical analyses

SPSS Statistics 22 will be used for the statistical analyses. Parametric and non-parametric tests will be used to determine if the 3 groups are comparable at baseline on 4 variables, 3 caregiver variables (gender, age and level of education) and 1 person with dementia variable (time since diagnosis). Variables that differ will be used as covariates in the subsequent analyses.

Cross-sectional analyses will be used to evaluate group differences at each of the individual time points (T2-T4) and include $\chi 2$ for categorical variables, the Mann-Whitney U test for ordinal data, and the Student t test or multivariate analysis of variance ((M)AN(C)OVA) for continuous dependent variables. Differences across the time points will be analyzed using multilevel analysis, which allows inclusion of all available data (i.e. also those from participants with missing data).

The predictive value of the determinants for the primary and secondary outcome measures at T2, T3, and T4 will be determined using multivariate regression analysis (2 time points) or multilevel analysis (> 2 time points). Potential predictors are defined as variables with at least a marginally significant

association ($p < .10$) with the outcome. Only these variables will be included in the subsequent analyses to determine the most important predictors. Effects with a 2-tailed $p < .05$ are considered statistically significant. Missing data will be imputed where possible. We will use the Bonferroni correction to correct for multiple comparisons.
A prediction model will be developed to define the most valuable variables for the effectivity of this intervention. Possible predictors are age, gender, relationship with the patient and hours of care.
The qualitative questions in the interviews will be analyzed using descriptive statistics and frequencies.

Sample size and power calculation
The sample size needed is calculated with G*Power, based on the main research question: does the simulator training increase the empathy of informal caregivers? Based on an alpha level of .05 and a power of .80, 64 participants per group are needed to be able to detect a medium difference ($d = 0.5$) between the groups. We expect about 10% drop-out during the 1-year follow-up period due to mortality of the caregivers or the person the caregivers care for, or due to refusal to continue participation. Therefore, we aim to include at least 71 participants in each group; 3*71 = 213 participants in total.

ETHICS AND DISSEMINATION

Ethical considerations
This study is non-invasive and imposes no risk on either the participating caregivers or the people with dementia. This protocol has been approved by the psychological ethical committees of both the Tilburg School of Social and Behavioral Sciences, Tilburg University and De Wever (a care organization for eldercare) in Tilburg, the Netherlands. Written informed consent is obtained from all participants, in accordance with the 'Helsinki Declaration' (Seoul Revision, 2008). The data is stored anonymously and only the primary researchers (LJ, RM, and MM) have access to the data. This study has been registered by The Dutch National Trial Register (NTR), number (TC): NTR5856.

Dissemination
The results obtained will be disseminated to the scientific and general public by publication in national and international (peer-reviewed) scientific and professional journals, as well as by presentations at conferences and meetings with professionals dealing with (informal caregivers of people with) dementia. First, a manuscript with the results of the primary study outcome (empathy) will be published in a peer-reviewed journal. Separate manuscripts will be written on the secondary research outcomes, and these will also be submitted for publication in peer-reviewed journals. The data will not be made public, assuring the study participants' privacy. Requests for data sharing will be considered on an individual basis, for appropriate research purposes only after completion of the trial and after publication of the primary manuscript.

DISCUSSION
This is the first study in which the effectivity of a mixed virtual reality dementia simulator is extensively tested in caregivers in a controlled trial. While multiple interventions for caregivers have been designed and tested[42], this is the first dementia simulator in which caregivers actually experience what it is like to have dementia, not only on a functional level, but also emotionally and socially. The focus on experience-based learning makes this intervention very practical.

Strong elements of this study are its longitudinal prospective design with multiple assessments. This is a useful addition to the existing effect studies into interventions for caregivers, which usually apply pre-

post designs which makes it impossible to know if these interventions work in the longer term. In addition, we include both quantitative (questionnaires) and qualitative (semi-structured interviews) measurements. Also, a control group is included which was not always the case in previous intervention studies with caregivers. The control group makes it possible to attribute the findings to the intervention, instead of to other variables such as elapsed time. A potential limitation is that due to practical reasons the participants were not randomized. The simulator was available for free for 5 weeks only (after which it was again made available for a financial compensation), in which we deemed it impossible to include enough caregivers for both the intervention and control group. Instead, the groups are recruited consecutively and we aim to statistically control for differing variables using covariates. These practical reasons were mainly of a financial nature, and are not associated with the availability of the intervention.

The recruitment of the control group took longer than the recruitment of the intervention group, see Figure 2. This is partly due to the fact that our existing networks were depleted once we started the recruitment of the control group, so new networks had to be formed. Another potential reason was that participants may have been less eager to participate because the compensation (the group training after completion of the study) is a much more long-term reward than participating in the simulator training approximately 1 week after inclusion.

In conclusion, we hope that this study will determine how effective (or not) the Into D'mentia training is on a variety of variables including empathy and caregiver burden. Furthermore, we believe that it has the potential to contribute to existing knowledge about caregivers. The dementia simulator is expected to be specifically effective in enhancing the quality of life of both caregivers and the people with dementia they care for by helping caregivers understand dementia better in a more personal way.

More informal caregivers than ever before are involved in the care for a family member or friend living with dementia. Helping them in their task should be a priority in health care services around the world. At the moment the Into D'mentia training is too expensive for many individual caregivers (the training costs €240,- per person). If it proves to be effective (on one or more outcomes) the next step would be to do a cost-effectiveness analyses and get it implemented into standard care, making it available for all caregivers and also for care professionals. The ultimate goal is to assist caregivers in the best possible way in their task of caring for their loved ones with dementia, a task most come unprepared to and a task that no one asks for.

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Contributors
LHJ, REM, BWJMJ, JR, RMD, and MMS contributed to study concept, planning and data acquisition, LHJ, REM and MMS will contribute to the statistical analyses, publication and dissemination of findings. LHJ wrote the first manuscript, all other authors provided critical feedback during the manuscript development and approved of the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing Interests
The authors declare that they have no competing interests

Ethics approval
Approval for this study was provided by the psychological ethical committees of both the Tilburg School of Social and Behavioral Sciences, Tilburg University (number EC-2015.25) and De Wever (a care organisation for eldercare) in Tilburg, the Netherlands. Written consent is obtained from all participants.

Data sharing statement
Data are sensitive and the first priority in sharing data will be protection of study participants' privacy. Therefore, this will not be a public use dataset. The authors will consider requests for data sharing on an individual basis, for appropriate research purposes, after publication of the major findings of the study.

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PLACEMENT FIGURE 1

PLACEMENT FIGURE 2

Figure 1. The simulator's goals

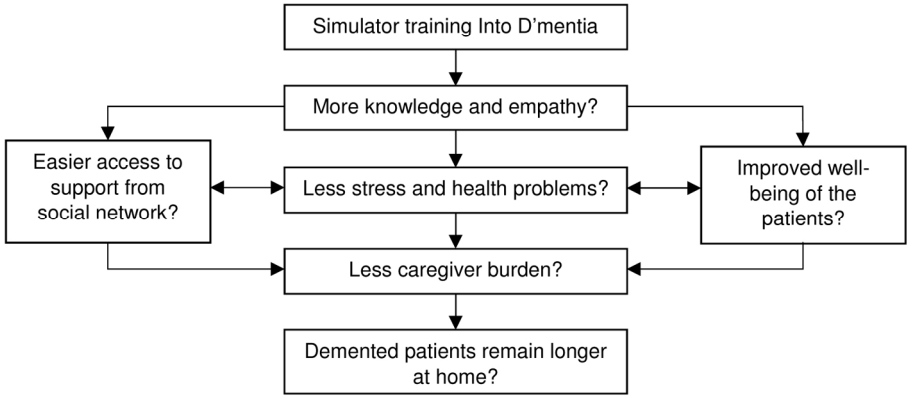

Figure 1. The simulator's goals

155x71mm (300 x 300 DPI)

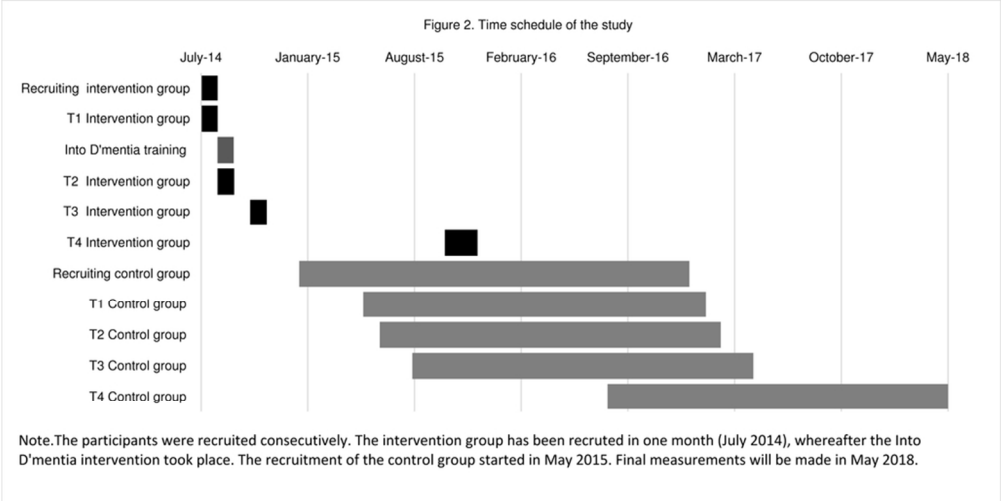

Figure 2. Time schedule of the study

87x43mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	-1 (title page)	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	3	
Methods				
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-10	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	10	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-9	
Bias	9	Describe any efforts to address potential sources of bias	9-11	
Study size	10	Explain how the study size was arrived at	10	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9-10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9-10
		(*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Testing the effectivity of the mixed virtual reality training Into D'mentia for informal caregivers of people with dementia: protocol for a longitudinal, quasi-experimental study.

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Testing the effectivity of the mixed virtual reality training Into D'mentia for informal caregivers of people with dementia: protocol for a longitudinal, quasi-experimental study.

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ABSTRACT

Introduction: Informal caregivers for people with dementia (hereafter: caregivers) often feel (over)burdened by the care for a loved one with dementia and this can have various deleterious effects on both caregivers and patients. Support for caregivers is urgently needed and for this reason a dementia simulator (Into D'mentia) was developed in which caregivers experience what it is like to have dementia. The simulator attempts to heighten caregivers' empathy and understanding for the patient and, in turn, diminish their own caregiver burden. The current study evaluates whether the simulator is effective on a number of outcomes.

Methods and analysis: A longitudinal, quasi-experimental study is ongoing in the Netherlands. We aim to recruit 142 caregivers in total divided over 2 groups: 71 caregivers in the intervention group and 71 caregivers in the control group. All participants will complete interviews and questionnaires at 4 time points; at baseline, 1 week, 2.5 months and 15 months after the training. The primary outcomes include: empathy, caregiver burden, caregiver's sense of competence, social reliance, anxiety, depression and caregivers' subjective and objective health.

Ethics and dissemination: This study is being carried out in agreement with the Declaration of Helsinki and the protocol has been approved by the local ethics committees.

Registration details: This study is registered with The Netherlands National Trial Register (number = NTR5856).

Keywords: dementia, informal caregiver, virtual reality, caregiver burden, empathy

Strengths and limitations of the study

Strengths

- It is a longitudinal, prospective design with multiple assessments. This is a useful addition to the existing effect studies into interventions for caregivers, which usually apply pre-post designs making it impossible to know if these interventions work in the longer term.
- We include both quantitative (questionnaires) and qualitative (semi-structured interviews) measurements.
- A control group is included which was not always the case in previous intervention studies with caregivers. The control group makes it possible to attribute the findings to the intervention, instead of to other variables such as elapsed time.

Limitations

- A potential limitation is that due to practical reasons the participants were not randomized. The simulator was available for free for 5 weeks only, in which we deemed it impossible to recruit enough caregivers for both the intervention and control group. Instead, the groups are recruited consecutively and we aim to statistically control for differing variables using covariates.

BACKGROUND

The number of people living with dementia worldwide is currently estimated at 35.6 million. This number will double by 2030 and more than triple by 2050[1]. In the Netherlands 260,000 people were diagnosed with dementia in 2014. 70% of these people live at home and are dependent on informal caregivers (hereafter: caregivers) for their daily care[2]. Caregivers are mostly unpaid spouses, sons, daughters, friends or relatives.

Although caregiving is satisfying for some caregivers[3-5], it can also be very burdensome[6, 7]. Caregivers often experience higher rates of depression[8], poorer physical and mental health[9-11], a lower sense of well-being, more social isolation[12] and more financial burden[13] than people who do not provide care. The likelihood of nursing home admission for the person with dementia rises when their caregiver becomes overburdened and can no longer cope[14]. An intervention which supports caregivers in their caregiving role is therefore very desirable.

In the past 10-15 years, several interventions have been developed to support caregivers. These include: training and education programs, support groups, counseling, web-based and multi-component interventions. These have been found to be moderately effective in improving the quality of care and competence of caregivers[15-17], diminishing caregiver burden[17, 18], health related problems [19, 20], stress[20, 21], improving the quality of life of both caregivers and their patients[22] and diminishing the dependency on professionals[17, 20]. However, most of these interventions lack practical tips and advice on how to apply the knowledge gained in daily life. The idea came to us that if caregivers could actually experience symptoms of dementia themselves they might understand their patients better and in turn have more empathy for them. With this hypothesis in mind the mixed virtual reality simulator 'Into D'mentia' was developed in 2010[23]. We also included education and the use of support groups in our training (these take place after the caregivers experience in the simulator) because these have been found to be beneficial in other interventions[24, 25].

The simulator's goal is to increase caregivers' knowledge and empathy for the person with dementia. It is hypothesized that this will lead to decreased stress levels, caregiver burden and health problems associated with caregiving in the caregivers themselves, and that this in turn will lead to the person with dementia living at home for longer before being institutionalized (see Figure 1). A better understanding of dementia has been found to promote the wellbeing of caregivers in a previous study[26]. In another study, when caregivers cared in a more empathetic way for the person with dementia, their own stress level was reduced[27]. Professionals who have more (versus those who have less) empathy have also been found to have fewer burn-outs and are more satisfied with their work as a professional caregiver, while the people with dementia under their care adhere better to therapy and have better health related outcomes[27, 28].

The aim of the current study is to assess the effectivity of the Into D'mentia simulator on a number of variables over time including: empathy, caregiver burden, feelings of competence of caregiving, depression and anxiety, the relationship between caregivers and their patients, and caregivers' health. This will be the first study that evaluates an intervention which attempts to simulate dementia. Here we describe the design and protocol of this study.

METHODS AND ANALYSES

Design

A longitudinal, quasi-experimental study with 2 groups is ongoing. The study began in 2014, the final measurements will be made in 2018. Participants are evaluated 4 times: 1 week before the Into D'mentia training (T1), and 1 week, 2.5 months and 15 months after the training (T2, T3, T4 respectively). The control group is tested at the same time intervals, starting at T1. Figure 2 shows a graph of the time schedule and important dates.

Study population

2 groups are created and consecutively recruited:

- The intervention group. This group receives the Into D'mentia simulator training (and is not prohibited from usual care).
  The group consists of informal caregivers of a relative, friend or spouse with dementia. The participants are recruited from de Wever in Tilburg, the Netherlands, an organization for eldercare; elderly federations; Alzheimer Nederland; case managers; centers for daytime activities for people with dementia and via social media.
  Inclusion criteria:
  - An informal caregiver for a spouse, family member, or friend with dementia; spending at least 8 hours a week caring for the patient who lives at home (not institutionalized).
  - At least 18 years old (no upper age limit).
  Exclusion criteria:
  - Physical disabilities which make entrance into the simulator impossible.
  - Severe communication disabilities which make understanding of the simulator impossible (e.g. insufficient understanding of the Dutch language, blindness or deafness).
  - Self-reported severe psychological or medical disabilities which make the simulator too confusing (including self-reported dementia).
- The control group. This group also consists of caregivers. The recruitment, inclusion and exclusion criteria are the same as for the intervention group. The only difference is that this group does not experience the intervention and as such is an attention-only group. This group is not prohibited from usual care. After completion of the study, a group meeting will be organized as a reward for participating in the study. During this meeting, professionals will provide information about dementia and the participants will have the opportunity to ask questions.

Procedure

Eligible participants receive oral and written information about the study from case managers, nurses, and supervisors at day-time activity centers; or only written information on social media. Eligible participants are invited to contact the researchers (LJ) by phone or e-mail if they have questions and to receive more information about the study. If they are interested in participating, the appointment for the first interview is scheduled and the questionnaires are sent. For the intervention group, an appointment for the intervention training is made at the same time. Written consent is also obtained. For the follow-up assessments (T2 – T4), participants are informed by letter, telephone or e-mail and invited to participate after which an appointment is scheduled.

For both the intervention and the control group, 4 measurements take place; for all 4 assessments a semi-structured interview is conducted and a questionnaire booklet is provided. The interviews are administered in a standardized way by trained neuropsychologists and take place either at the participant's home or at Tilburg University depending on the caregivers' preference. The questionnaire booklet is sent to the participants before the appointment for the interview with the request that they complete it at home and bring it with them to the interview when they can receive help should any problems arise.

The questionnaires and interviews are identical for the 2 groups. The only exception being for the control group, where questions about the simulator training are not relevant and therefore omitted.

Intervention

The intervention is a mixed-reality dementia simulator training. The training consists of 3 parts: the simulation, an individual conversation with the trainer immediately after the simulation and a group meeting with the other participants 1-2 weeks later. In the simulator, the participants experience what it is like to have dementia. The training was developed based on literature reviews and on talks with caregivers, professionals and a number of people with dementia[23]. The caregivers, professionals and people with dementia were also involved in the process of developing, altering, and improving the intervention. They all approved of the final simulator, which we are currently using in this study. The simulator training takes place in a portable unit in which a little front yard, a bathroom and a kitchen are built. After a short, individual introduction, the participant enters the simulator unit. The participant wears a speaker vest, with microphones from which their ''inner voice'' tells the story. This inner voice gives them specific instructions, for example to turn on the radio which then appears to not work properly. The participant's ''daughter'' is projected on a screen using a beamer and she behaves like many caregivers do, for example talking about the patient while the patient is in the room, getting frustrated et cetera. Several audiovisual elements make the simulator interactive, allowing the participant to make choices and thereby influence the storyline. Empathic reactions of negative situations (like caring for a relative with pain, or in this case, dementia), can lead to stress, or negative changes in neural networks[29]. To ensure the safety and well-being of the participants, immediately after the training an individual conversation with the trainer is organized. During this conversation, the participants discuss their experiences in the simulator and the trainer comforts the participants if needed. If the participants are heavily distressed, they can also telephone the research team (all trained psychologists) for help. The participants are encouraged to discuss their experiences in the simulator with family members or friends regardless of immediate stress reactions. The participants can call the research team if they experience any negative reactions which cannot wait until the group meeting. A group meeting with 8-12 other participants is organized 1-2 weeks after the training in order to help them to better understand and to implement their experiences and new knowledge into their daily lives. During this group meeting, experiences in the simulator are described in more detail and are put into perspective. In addition, professionals give information about dementia and some practical tips are shared. At the same time, the caregivers can learn from each other's experiences.

Measures

Tables 1 and 2 give an overview of the variables assessed and instruments used at each time point. Short questionnaires (or self-made questions) were specifically chosen in order to reduce the time (about 45 minutes in total) required to complete, because caregivers are typically busy and 82%

overburdened[30]. The interviews take about 45 minutes to complete, leading to a time-investment of approximately 90 minutes per measurement per caregiver.

Outcomes

Primary outcomes

The primary outcomes chosen to assess how effective the Into D'mentia simulator are as follows: empathy, caregiver burden, depression and anxiety, the quality of the relationship between caregiver and patient, and caregiver's sense of competence.

- To measure empathy, the most important primary outcome, the Interpersonal Reactivity Index (IRI)[31] is used. The IRI asks subjects to rate 28 items on several empathy-related statements on a 5-point Likert scale ranging from 'does not describe me well' to 'describes me very well'. The 28 items are clustered into 4 subscales, each made up of 7 different items: perspective taking, fantasy, empathic concern, and personal distress, leading to a multidimensional approach to empathy. The Cronbach's alpha for the subscales ranges from .70 to .76[32].
- Caregiver burden is evaluated by the Caregiver Reaction Assessment Dutch (CRA-D)[33]. The CRA-D measures both negative and positive reactions to caregiving. The questionnaire consists of 24 items, clustered into 5 dimensions: the impact of caregiving on disrupted schedule, financial problems, lack of family support, health problems, and the impact of caregiving on caregiver's self-esteem, with Cronbach's alpha ranging from .62 to .83[34]. The subject reports to what extent he or she agrees with the 24 statements on a 5-point scale.
- Anxiety and depression are measured using the Hospital Anxiety and Depression Scale (HADS)[35]. The HADS comprises 7 questions for anxiety and 7 questions for depression and takes 2 to 5 minutes to complete. The items are rated on a 4-point scale (0-3) and concern anxiety and depression symptoms from the last week. The scores on the subscales are added up and a cut-off score of 8 is used to indicate depressive or anxiety complaints. For the anxiety subscale, Cronbach's alpha ranges from .76 to .93, for the depression subscale it ranges from .72 to .90 in different studies[36].
- The quality of the relationship between caregiver and patient is evaluated using 2 questionnaires. The first is the Relationship Quality Index (RQI), which consists of 5 questions which can be answered on a 7-point Likert scale. The maximum score is 35. A higher score indicates a higher quality relationship[37]. The second questionnaire to measure relationship quality is based on the Affectual Solidarity (AS) questionnaire used for the Longitudinal Study of Generations (LSOG)[38], which in this study is named Quality of the Relationship (QoR). This questionnaire evaluates 2 domains: Current relationship quality (QoR-current) (6 items), and Change in relationship quality (QoR-change) (5 items). The 6 items of the QoR-current are evaluated on a 4-point scale. Scores range from 6 to 24, with a higher score indicating a better relationship quality. The 5 items of the QoR-change are statements regarding how much things have changed since the dementia diagnosis of a loved one. The statements are evaluated on a 5-point scale, the total score ranges from 5 to 25, with a higher score indicating a lower relationship quality.
- Caregiver's sense of competence is assessed by the Short Sense of Competence Questionnaire (SSCQ), which consists of 7 items, rated according to a 5-point Likert scale (1-5). The items are clustered into 3 domains: Lack of satisfaction with the person with dementia as a recipient of care; Lack of satisfaction with one's own performance as a carer; and Consequences of involvement in care for the personal life of the carer. The total score ranges from 0 to 35, with a Cronbach's alpha of .76[39].

Secondary outcomes

Secondary outcomes include for the caregivers: social reliance (use of social networks and participation)

subjective and objective health, life events, quality of life and quality of sleep. The living situation of the person with dementia will also be assessed.

- Social reliance is measured by the Dutch version of the Inventory for Social Reliance. The questionnaire evaluates both the quantitative and qualitative aspects of social support. The quantitative part consists of 2 items; the number of good friends and the number of acquaintances in the participants' neighborhood. The qualitative part entails 11 items; rated according to a 4-point Likert scale, which cover 3 aspects of social support: perceived emotional support, actual emotional support, mutual visiting and 1 rest item[40, 41].
- Subjective health is evaluated by asking the caregivers if they had cognitive, depressive or anxiety complaints in the last 4 weeks. Objective health in the caregivers is assessed during the semi-structured interviews using the following (separate) measures (relying on self-report): the number of medications the caregiver personally uses, the number of hospital admissions, visits to the general practitioner, and visits to the hospital in the last month.
- To assess life events, the participants answer the following self-made written question concerning the presence and impact of a positive or negative life event 'In the past month, did something happen in your life which had a major impact on you? This may be something either pleasant or sad'. The subjects can choose between 'no' or 'yes, namely.. '. If the answer is yes, the next question is what the total impact of the experience is, which the subject can rate according to a 5-point Likert scale ranging from 'very negative impact' to 'very positive impact'.
- Quality of life and quality of sleep are both evaluated using 1 self-made Likert scale. The subject is asked to rate their quality of sleep and quality of life at 'this' moment in their lives, by putting a cross on this line:

0 25 50 75 100
|_____|_____|_____|_____|
Very bad Very good

- The living situation of the person with dementia is assessed by asking the caregivers if the person still lives at home or if he or she has been institutionalized.

Table 1. Primary outcomes

	Variable/Instrument	T1	T2	T3	T4
Primary outcomes					
Empathy	Interpersonal Reactivity Index[31]	X	X	X	X
Caregiver burden	Caregiver Reaction Assessment - Dutch[33]	X	X	X	X
Depressive complaints	Hospital Anxiety and Depression Scale – subscale depression[35]	X	X	X	X
Anxiety complaints	Hospital Anxiety and Depression Scale – subscale anxiety[35]	X	X	X	X
Quality of the relationship	Relationship Quality Index[37]	X	X	X	X
	Quality of the Relationship[38]	X	X	X	X
Caregiver's sense of competence	Short Sense of Competence Questionnaire[39]	X	X	X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3.

Table 2. Secondary outcomes

	Variable/Instrument		T1	T2	T3	T4
Social reliance	Inventory for Social Reliance[40]		X	X	X	X
Subjective health	Cognitive complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience cognitive complaints?'	X			
		Self-made item: 'In the previous month, have you experienced cognitive complaints?'	X	X	X	X
	Depressive complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience depressive complaints?'	X			
		Self-made item: 'In the previous month, have you experienced depressive complaints?'	X	X	X	X
	Anxiety complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience anxiety complaints?'	X			
		Self-made item: 'In the previous month, have you experienced anxiety complaints?'	X	X	X	X
Objective health	Number of hospital admissions		X	X	X	X
	Number of hospital visits		X	X	X	X
	Number of GP visits		X	X	X	X
Life events	Self-made item concerning the presence and impact of a positive of negative life event: 'Last month, did something happen in your life which had a major impact on you? This may be something either pleasant or sad'		X	X	X	X
Quality of life	Self-made item concerning the quality of life of the caregivers: 'How would you rate your quality of life on this point in your life?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good)		X	X	X	X
Quality of sleep	Self-made item about the quality of sleep: 'Before the dementia of your spouse/friend/relative, how would you have rated your quality of sleep?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good).		X			
	Self-made item about the quality of sleep: 'How would you have rated your quality of sleep on this point in your life?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good).		X	X	X	X
Health and living situation patient	Self-made item concerning the progression of the dementia of the patient: 'How is he or she doing compared to the time of the last interview?' The possible answers are better, the same or worse, than the last interview.			X	X	X
	Self-made item concerning the living situation of the patient: 'Has something changed in the living situation of the patient since the last interview?'			X	X	X
	Self-made item about the concerns of the caregivers about the dementia of the patient: 'Do you have any new concerns about the dementia since the last interview?'			X	X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3.

Possible determinants/confounders

A wide range of possible determinants/confounders (factors in the prediction model and/or covariates) are additionally taken into account, based on what is currently known from the literature about caregivers. These include: sociodemographic variables, medicine use of both caregivers and the people with dementia they care for, and clinical variables regarding the dementia such as the type and time since diagnosis. These data rely on self-report of the informal caregiver. Finally, a couple of qualitative variables are also assessed, e.g. subjective experiences with the simulator (for the intervention group only). Table 3 lists the specific variables assessed and instruments used.

Table 3. Possible determinants/confounders

	Variable/Instrument	T1	T2	T3	T4
Sociodemographic and clinical variables of the caregivers					
Age, gender, education, employment status		X			
Medicine use		X			
Presence and severity of physical disabilities	Self-made question: 'Do you have any physical disabilities and if so, to what extent do these interfere with caregiving?'	X			
Presence and severity of psychological disabilities	Self-made question: 'Do you have any psychological disabilities and if so, to what extent do these interfere with caregiving?'	X			
Variables concerning caregiving	Relationship with the patient with dementia (spouse/daughter/son/something else)	X			
	Distance to the patient (shares household/walking distance/in the same city/in a different city)	X			
	Days providing care a week	X			
	Hours providing care a week	X			
	Years since first time providing care for this patient	X			
	Support of professionals (e.g. housekeeper, case-manager)	X			
	Perceived support of friends or family	X			
Clinical variables of the patient with dementia					
Diagnosis	Alzheimer's disease/Vascular dementia/Parkinson's Disease Dementia/Frontotemporal Dementia/other/unknown	X			
Time since diagnosis (in years)		X			
Medicine use		X			
Comorbidities	Physical comorbidities	X			
	Psychological comorbidities	X			
Support of professional (e.g. physiotherapist)		X			
Self-made items regarding the subjective effectivity of the training*					
'Does the simulator give an accurate reflection of what a demented person goes through?'			X	X	X
'Did the simulator meet your expectations?'			X	X	X
'Do you think the simulator is useful?'			X	X	X
'Did you feel supported by the experiences and stories of the other participants in the group meeting?'			X	X	X
'Did the group meeting meet your expectations?'			X	X	X
'Do you think the group meeting is useful?'			X	X	X
'Did the whole training (simulator and group meeting together) had a personal impact on you?'			X	X	X
'Do you think that the whole training helps you to be a more effective caregiver?'			X	X	X
'Do you think the whole training has helped you to understand your spouse/relative/friend?'			X	X	X
'Do you think that you are better prepared for what is going to happen in the future?'			X	X	X
'Are you surer of your qualities because of the training?'			X	X	X
'Did you learn anything from the training? And if yes, what?'			X	X	X
'Do you do anything different in caring because of the training? And if yes, what?			X	X	X
'Do you think the training missed anything? And if yes, what?'				X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3. *: Questions for the intervention group only.

Planned statistical analyses

SPSS Statistics 22 will be used for the statistical analyses. Parametric and non-parametric tests will be used to determine if the 2 groups are comparable at baseline on 4 variables, 3 caregiver variables (gender, age and level of education) and 1 person with dementia variable (time since diagnosis). Variables that differ will be used as covariates in the subsequent analyses.

Cross-sectional analyses will be used to evaluate group differences at each of the individual time points (T2-T4) and include $\chi 2$ for categorical variables, the Mann-Whitney U test for ordinal data, and the Student t test or multivariate analysis of variance ((M)AN(C)OVA) for continuous dependent variables. Differences across the time points will be analyzed using multilevel analysis, which allows inclusion of all

available data (i.e. also those from participants with missing data).
The predictive value of the determinants for the primary and secondary outcome measures at T2, T3, and T4 will be determined using multivariate regression analysis (2 time points) or multilevel analysis (> 2 time points). Potential predictors are defined as variables with at least a marginally significant association ($p < .10$) with the outcome. Only these variables will be included in the subsequent analyses to determine the most important predictors. Effects with a 2-tailed $p < .05$ are considered statistically significant. Missing data will be imputed where possible. We will use the Bonferroni correction to correct for multiple comparisons.
A prediction model will be developed to define the most valuable variables for the effectivity of this intervention. Possible predictors are age, gender, relationship with the patient and hours of care.
The qualitative questions in the interviews will be analyzed using descriptive statistics and frequencies.

Sample size and power calculation

The sample size needed is calculated with G*Power, based on the main research question: does the simulator training increase the empathy of informal caregivers? Based on an alpha level of .05 and a power of .80, 64 participants per group are needed to be able to detect a medium difference ($d = 0.5$) between the groups. We expect about 10% drop-out during the 1-year follow-up period due to mortality of the caregivers or the person the caregivers care for, or due to refusal to continue participation. Therefore, we aim to include at least 71 participants in each group; 2*71 = 142 participants in total.

ETHICS AND DISSEMINATION

Ethical considerations

This study is non-invasive and imposes no risk on either the participating caregivers or the people with dementia. This protocol has been approved by the psychological ethical committees of both the Tilburg School of Social and Behavioral Sciences, Tilburg University and De Wever (a care organization for eldercare) in Tilburg, the Netherlands. Written informed consent is obtained from all participants, in accordance with the 'Helsinki Declaration' (Seoul Revision, 2008). The data is stored anonymously and only the primary researchers (LHJ, REM, and MMS) have access to the data. This study has been registered by The Dutch National Trial Register (NTR), number (TC): NTR5856.

Dissemination

The results obtained will be disseminated to the scientific and general public by publication in national and international (peer-reviewed) scientific and professional journals, as well as by presentations at conferences and meetings with professionals dealing with (informal caregivers of people with) dementia. First, a manuscript with the results of the primary study outcome (empathy) will be published in a peer-reviewed journal. Separate manuscripts will be written on the secondary research outcomes, and these will also be submitted for publication in peer-reviewed journals. The data will not be made public, assuring the study participants' privacy. Requests for data sharing will be considered on an individual basis, for appropriate research purposes only, after completion of the trial, and after publication of the primary manuscript.

DISCUSSION

This is the first study in which the effectivity of a mixed virtual reality dementia simulator is extensively tested in caregivers in a controlled trial. While multiple interventions for caregivers have been designed and tested[42], this is the first dementia simulator in which caregivers actually experience what it is like

to have dementia, not only on a functional level, but also emotionally and socially. The focus on experience-based learning makes this intervention very practical.

Strong elements of this study are its longitudinal prospective design with multiple assessments. This is a useful addition to the existing effect studies into interventions for caregivers, which usually apply pre-post designs which makes it impossible to know if these interventions work in the longer term. In addition, we include both quantitative (questionnaires) and qualitative (semi-structured interviews) measurements. We are aware that there are many variables, but we feel that it is necessary to take them all into account because many factors are involved in caregiver burden and need to be considered in any attempt to ultimately figure out which are important. Also, a control group is included which was not always the case in previous intervention studies with caregivers. The control group makes it possible to attribute the findings to the intervention, instead of to other variables such as elapsed time. A potential limitation is that due to practical reasons the participants were not randomized. The simulator was available for free for 5 weeks only (after which it was again made available for a financial compensation), in which we deemed it impossible to include enough caregivers for both the intervention and control group. Instead, the groups are recruited consecutively and we aim to statistically control for differing variables using covariates. These practical reasons were mainly of a financial nature; the intervention is freely available for the public at a cost.
The recruitment of the control group took longer than the recruitment of the intervention group, see Figure 2. This is partly due to the fact that our existing networks were depleted once we started the recruitment of the control group, so new networks had to be formed. Another potential reason was that these (control) participants may have been less eager to participate because they had to wait until the end of the study for their 'reward' (the group meeting).

In conclusion, we hope that this study will determine how effective (or not) the Into D'mentia training is on a variety of variables including empathy and caregiver burden. Furthermore, we believe that it has the potential to contribute to existing knowledge about caregivers. The dementia simulator is expected to be specifically effective in enhancing the quality of life of both caregivers and the people with dementia they care for by helping caregivers understand dementia better in a more personal way.

More informal caregivers than ever before are involved in the care for a family member or friend living with dementia. Helping them in their task should be a priority in health care services around the world. At the moment the Into D'mentia training is too expensive for many individual caregivers (the training costs €240,- per person). If it proves to be effective (on one or more outcomes) the next step would be to do a cost-effectiveness analyses and get it implemented into standard care, making it available for all caregivers and also for care professionals. The ultimate goal is to assist caregivers in the best possible way in their task of caring for their loved ones with dementia, a task most come unprepared to and a task that no one asks for.

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Contributors
LHJ, REM, BWJMJ, JR, RMD, and MMS contributed to study concept, planning and data acquisition, LHJ, REM and MMS will contribute to the statistical analyses, publication and dissemination of findings. LHJ wrote the first manuscript, all other authors provided critical feedback during the manuscript development and approved of the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing Interests
The authors declare that they have no competing interests.

Ethics approval
Approval for this study was provided by the psychological ethical committees of both the Tilburg School of Social and Behavioral Sciences, Tilburg University (number EC-2015.25) and De Wever (a care organisation for eldercare) in Tilburg, the Netherlands. Written consent is obtained from all participants.

Data sharing statement
Data are sensitive and the first priority in sharing data will be protection of study participants' privacy. Therefore, this will not be a public use dataset. The authors will consider requests for data sharing on an individual basis, for appropriate research purposes, after publication of the major findings of the study.

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PLACEMENT FIGURE 1

PLACEMENT FIGURE 2

Figure 1. The simulator's goals

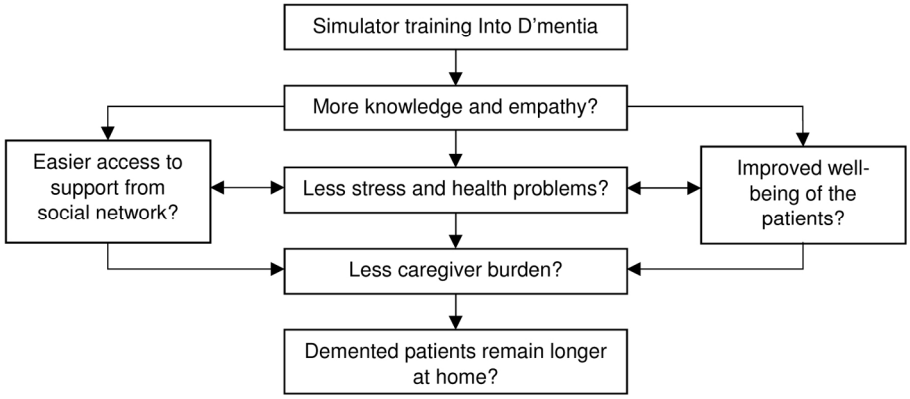

Figure 1. The simulator's goals

155x71mm (300 x 300 DPI)

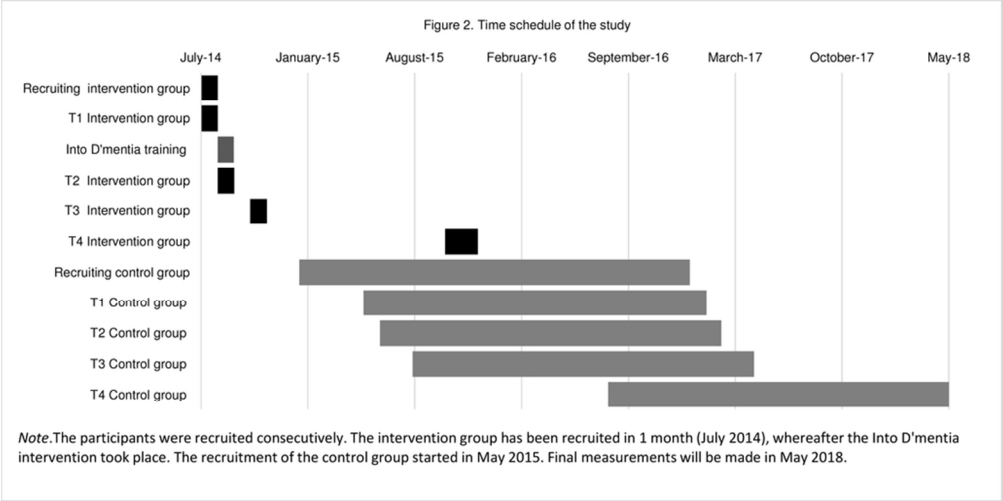

Figure 2. Time schedule of the study

87x43mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	-1 (title page)	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	3	
Methods				
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-10	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	10	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-9	
Bias	9	Describe any efforts to address potential sources of bias	9-11	
Study size	10	Explain how the study size was arrived at	10	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9-10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9-10
		(*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Testing the effectivity of the mixed virtual reality training Into D'mentia for informal caregivers of people with dementia: protocol for a longitudinal, quasi-experimental study.

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ABSTRACT

Introduction: Informal caregivers for people with dementia (hereafter: caregivers) often feel (over)burdened by the care for a loved one with dementia and this can have various deleterious effects on both caregivers and patients. Support for caregivers is urgently needed and for this reason a dementia simulator (Into D'mentia) was developed in which caregivers experience what it is like to have dementia. The simulator attempts to heighten caregivers' empathy and understanding for the patient and, in turn, diminish their own caregiver burden. The current study evaluates whether the simulator is effective on a number of outcomes.

Methods and analysis: A longitudinal, quasi-experimental study is ongoing in the Netherlands. We aim to recruit 142 caregivers in total divided over 2 groups: 71 caregivers in the intervention group and 71 caregivers in the control group. All participants will complete interviews and questionnaires at 4 time points; at baseline, 1 week, 2.5 months and 15 months after the training. The primary outcomes include: empathy, caregiver burden, caregiver's sense of competence, social reliance, anxiety, depression and caregivers' subjective and objective health.

Ethics and dissemination: This study is being carried out in agreement with the Declaration of Helsinki and the protocol has been approved by the local ethics committees.

Registration details: This study is registered with The Netherlands National Trial Register (number = NTR5856).

Keywords: dementia, informal caregiver, virtual reality, simulation, caregiver burden, empathy

Strengths and limitations of the study

Strengths

- It is a longitudinal, prospective design with multiple assessments. This is a useful addition to the existing effect studies into interventions for caregivers, which usually apply pre-post designs making it impossible to know if these interventions work in the longer term.
- We include both quantitative (questionnaires) and qualitative (semi-structured interviews) measurements.
- A control group is included which was not always the case in previous intervention studies with caregivers. The control group makes it possible to attribute the findings to the intervention, instead of to other variables such as elapsed time.

Limitations

- A potential limitation is that due to practical reasons the participants were not randomized. The simulator was available for free for 5 weeks only, in which we deemed it impossible to recruit enough caregivers for both the intervention and control group. Instead, the groups are recruited consecutively and we aim to statistically control for differing variables using covariates.

BACKGROUND

The number of people living with dementia worldwide is currently estimated at 35.6 million. This number will double by 2030 and more than triple by 2050[1]. In the Netherlands 260,000 people were diagnosed with dementia in 2014. 70% of these people live at home and are dependent on informal caregivers (hereafter: caregivers) for their daily care[2]. Caregivers are mostly unpaid spouses, sons, daughters, friends or relatives.

Although caregiving is satisfying for some caregivers[3-5], it can also be very burdensome[6, 7]. Caregivers often experience higher rates of depression[8], poorer physical and mental health[9-11], a lower sense of well-being, more social isolation[12] and more financial burden[13] than people who do not provide care. The likelihood of nursing home admission for the person with dementia rises when their caregiver becomes overburdened and can no longer cope[14]. An intervention which supports caregivers in their caregiving role is therefore very desirable.

In the past 10-15 years, several interventions have been developed to support caregivers. These include: training and education programs, support groups, counseling, web-based and multi-component interventions. These have been found to be moderately effective in improving the quality of care and competence of caregivers[15-17], diminishing caregiver burden[17, 18], health related problems [19, 20], stress[20, 21], improving the quality of life of both caregivers and their patients[22] and diminishing the dependency on professionals[17, 20]. However, most of these interventions lack practical tips and advice on how to apply the knowledge gained in daily life. The idea came to us that if caregivers could actually experience symptoms of dementia themselves they might understand their patients better and in turn have more empathy for them. With this hypothesis in mind the mixed virtual reality simulator 'Into D'mentia' was developed in 2010[23]. We also included education and the use of support groups in our training (these take place after the caregivers experience in the simulator) because these have been found to be beneficial in other interventions[24, 25].

The simulator's goal is to increase caregivers' knowledge and empathy for the person with dementia. It is hypothesized that this will lead to decreased stress levels, caregiver burden and health problems associated with caregiving in the caregivers themselves, and that this in turn will lead to the person with dementia living at home for longer before being institutionalized (see Figure 1). A better understanding of dementia has been found to promote the wellbeing of caregivers in a previous study[26]. In another study, when caregivers cared in a more empathetic way for the person with dementia, their own stress level was reduced[27]. Professionals who have more (versus those who have less) empathy have also been found to have fewer burn-outs and are more satisfied with their work as a professional caregiver, while the people with dementia under their care adhere better to therapy and have better health related outcomes[27, 28].

The aim of the current study is to assess the effectivity of the Into D'mentia simulator on a number of variables over time including: empathy, caregiver burden, feelings of competence of caregiving, depression and anxiety, the relationship between caregivers and their patients, and caregivers' health. This will be the first study that evaluates an intervention which attempts to simulate dementia. Here we describe the design and protocol of this study.

METHODS AND ANALYSES

Design

A longitudinal, quasi-experimental study with 2 groups is ongoing. The study began in 2014, the final measurements will be made in 2018. Participants are evaluated 4 times: 1 week before the Into D'mentia training (T1), and 1 week, 2.5 months and 15 months after the training (T2, T3, T4 respectively). The control group is tested at the same time intervals, starting at T1. Figure 2 shows a graph of the time schedule and important dates.

Study population

2 groups are created and consecutively recruited:

- The intervention group. This group receives the Into D'mentia simulator training (and is not prohibited from usual care).
  The group consists of informal caregivers of a relative, friend or spouse with dementia. The participants are recruited from de Wever in Tilburg, the Netherlands, an organization for eldercare; elderly federations; Alzheimer Nederland; case managers; centers for daytime activities for people with dementia and via social media.
  Inclusion criteria:
  - An informal caregiver for a spouse, family member, or friend with dementia; spending at least 8 hours a week caring for the patient who lives at home (not institutionalized).
  - At least 18 years old (no upper age limit).
  Exclusion criteria:
  - Physical disabilities which make entrance into the simulator impossible.
  - Severe communication disabilities which make understanding of the simulator impossible (e.g. insufficient understanding of the Dutch language, blindness or deafness).
  - Self-reported severe psychological or medical disabilities which make the simulator too confusing (including self-reported dementia).
- The control group. This group also consists of caregivers. The recruitment, inclusion and exclusion criteria are the same as for the intervention group. The only difference is that this group does not experience the intervention and as such is an attention-only group. This group is not prohibited from usual care. After completion of the study, a group meeting will be organized as a reward for participating in the study. During this meeting, professionals will provide information about dementia and the participants will have the opportunity to ask questions.

Procedure

Eligible participants receive oral and written information about the study from case managers, nurses, and supervisors at day-time activity centers; or only written information on social media. Eligible participants are invited to contact the researchers (LJ) by phone or e-mail if they have questions and to receive more information about the study. If they are interested in participating, the appointment for the first interview is scheduled and the questionnaires are sent. For the intervention group, an appointment for the intervention training is made at the same time. Written consent is also obtained. For the follow-up assessments (T2 – T4), participants are informed by letter, telephone or e-mail and invited to participate after which an appointment is scheduled.

For both the intervention and the control group, 4 measurements take place; for all 4 assessments a semi-structured interview is conducted and a questionnaire booklet is provided. The interviews are administered in a standardized way by trained neuropsychologists and take place either at the participant's home or at Tilburg University depending on the caregivers' preference. The questionnaire booklet is sent to the participants before the appointment for the interview with the request that they complete it at home and bring it with them to the interview when they can receive help should any problems arise.

The questionnaires and interviews are identical for the 2 groups. The only exception being for the control group, where questions about the simulator training are not relevant and therefore omitted.

Intervention

The intervention is a mixed-reality dementia simulator training. The training consists of 3 parts: the simulation, an individual conversation with the trainer immediately after the simulation and a group meeting with the other participants 1-2 weeks later. In the simulator, the participants experience what it is like to have dementia. The training was developed based on literature reviews and on talks with caregivers, professionals and a number of people with dementia[23]. The caregivers, professionals and people with dementia were also involved in the process of developing, altering, and improving the intervention. They all approved of the final simulator, which we are currently using in this study. The simulator training takes place in a portable unit in which a little front yard, a bathroom and a kitchen are built. After a short, individual introduction, the participant enters the simulator unit. The participant wears a speaker vest, with microphones from which their ''inner voice'' tells the story. This inner voice gives them specific instructions, for example to turn on the radio which then appears to not work properly. The participant's ''daughter'' is projected on a screen using a beamer and she behaves like many caregivers do, for example talking about the patient while the patient is in the room, getting frustrated et cetera. Several audiovisual elements make the simulator interactive, allowing the participant to make choices and thereby influence the storyline. Empathic reactions of negative situations (like caring for a relative with pain, or in this case, dementia), can lead to stress, or negative changes in neural networks[29]. To ensure the safety and well-being of the participants, immediately after the training an individual conversation with the trainer is organized. During this conversation, the participants discuss their experiences in the simulator and the trainer comforts the participants if needed. If the participants are heavily distressed, they can also telephone the research team (all trained psychologists) for help. The participants are encouraged to discuss their experiences in the simulator with family members or friends regardless of immediate stress reactions. The participants can call the research team if they experience any negative reactions which cannot wait until the group meeting. A group meeting with 8-12 other participants is organized 1-2 weeks after the training in order to help them to better understand and to implement their experiences and new knowledge into their daily lives. During this group meeting, experiences in the simulator are described in more detail and are put into perspective. In addition, professionals give information about dementia and some practical tips are shared. At the same time, the caregivers can learn from each other's experiences.

Measures

Tables 1 and 2 give an overview of the variables assessed and instruments used at each time point. Short questionnaires (or self-made questions) were specifically chosen in order to reduce the time (about 45 minutes in total) required to complete, because caregivers are typically busy and 82%

overburdened[30]. The interviews take about 45 minutes to complete, leading to a time-investment of approximately 90 minutes per measurement per caregiver.

Outcomes

Primary outcomes

The primary outcomes chosen to assess how effective the Into D'mentia simulator are as follows: empathy, caregiver burden, depression and anxiety, the quality of the relationship between caregiver and patient, and caregiver's sense of competence.

- To measure empathy, the most important primary outcome, the Interpersonal Reactivity Index (IRI)[31] is used. The IRI asks subjects to rate 28 items on several empathy-related statements on a 5-point Likert scale ranging from 'does not describe me well' to 'describes me very well'. The 28 items are clustered into 4 subscales, each made up of 7 different items: perspective taking, fantasy, empathic concern, and personal distress, leading to a multidimensional approach to empathy. The Cronbach's alpha for the subscales ranges from .70 to .76[32].
- Caregiver burden is evaluated by the Caregiver Reaction Assessment Dutch (CRA-D)[33]. The CRA-D measures both negative and positive reactions to caregiving. The questionnaire consists of 24 items, clustered into 5 dimensions: the impact of caregiving on disrupted schedule, financial problems, lack of family support, health problems, and the impact of caregiving on caregiver's self-esteem, with Cronbach's alpha ranging from .62 to .83[34]. The subject reports to what extent he or she agrees with the 24 statements on a 5-point scale.
- Anxiety and depression are measured using the Hospital Anxiety and Depression Scale (HADS)[35]. The HADS comprises 7 questions for anxiety and 7 questions for depression and takes 2 to 5 minutes to complete. The items are rated on a 4-point scale (0-3) and concern anxiety and depression symptoms from the last week. The scores on the subscales are added up and a cut-off score of 8 is used to indicate depressive or anxiety complaints. For the anxiety subscale, Cronbach's alpha ranges from .76 to .93, for the depression subscale it ranges from .72 to .90 in different studies[36].
- The quality of the relationship between caregiver and patient is evaluated using 2 questionnaires. The first is the Relationship Quality Index (RQI), which consists of 5 questions which can be answered on a 7-point Likert scale. The maximum score is 35. A higher score indicates a higher quality relationship[37]. The second questionnaire to measure relationship quality is based on the Affectual Solidarity (AS) questionnaire used for the Longitudinal Study of Generations (LSOG)[38], which in this study is named Quality of the Relationship (QoR). This questionnaire evaluates 2 domains: Current relationship quality (QoR-current) (6 items), and Change in relationship quality (QoR-change) (5 items). The 6 items of the QoR-current are evaluated on a 4-point scale. Scores range from 6 to 24, with a higher score indicating a better relationship quality. The 5 items of the QoR-change are statements regarding how much things have changed since the dementia diagnosis of a loved one. The statements are evaluated on a 5-point scale, the total score ranges from 5 to 25, with a higher score indicating a lower relationship quality.
- Caregiver's sense of competence is assessed by the Short Sense of Competence Questionnaire (SSCQ), which consists of 7 items, rated according to a 5-point Likert scale (1-5). The items are clustered into 3 domains: Lack of satisfaction with the person with dementia as a recipient of care; Lack of satisfaction with one's own performance as a carer; and Consequences of involvement in care for the personal life of the carer. The total score ranges from 0 to 35, with a Cronbach's alpha of .76[39].

Secondary outcomes

Secondary outcomes include for the caregivers: social reliance (use of social networks and participation)

subjective and objective health, life events, quality of life and quality of sleep. The living situation of the person with dementia will also be assessed.

- Social reliance is measured by the Dutch version of the Inventory for Social Reliance. The questionnaire evaluates both the quantitative and qualitative aspects of social support. The quantitative part consists of 2 items; the number of good friends and the number of acquaintances in the participants' neighborhood. The qualitative part entails 11 items; rated according to a 4-point Likert scale, which cover 3 aspects of social support: perceived emotional support, actual emotional support, mutual visiting and 1 rest item[40, 41].
- Subjective health is evaluated by asking the caregivers if they had cognitive, depressive or anxiety complaints in the last 4 weeks. Objective health in the caregivers is assessed during the semi-structured interviews using the following (separate) measures (relying on self-report): the number of medications the caregiver personally uses, the number of hospital admissions, visits to the general practitioner, and visits to the hospital in the last month.
- To assess life events, the participants answer the following self-made written question concerning the presence and impact of a positive or negative life event 'In the past month, did something happen in your life which had a major impact on you? This may be something either pleasant or sad'. The subjects can choose between 'no' or 'yes, namely.. '. If the answer is yes, the next question is what the total impact of the experience is, which the subject can rate according to a 5-point Likert scale ranging from 'very negative impact' to 'very positive impact'.
- Quality of life and quality of sleep are both evaluated using 1 self-made Likert scale. The subject is asked to rate their quality of sleep and quality of life at 'this' moment in their lives, by putting a cross on this line:

0 25 50 75 100
|_____|_____|_____|_____|
Very bad Very good

- The living situation of the person with dementia is assessed by asking the caregivers if the person still lives at home or if he or she has been institutionalized.

Table 1. Primary outcomes

	Variable/Instrument	T1	T2	T3	T4
Primary outcomes					
Empathy	Interpersonal Reactivity Index[31]	X	X	X	X
Caregiver burden	Caregiver Reaction Assessment - Dutch[33]	X	X	X	X
Depressive complaints	Hospital Anxiety and Depression Scale – subscale depression[35]	X	X	X	X
Anxiety complaints	Hospital Anxiety and Depression Scale – subscale anxiety[35]	X	X	X	X
Quality of the relationship	Relationship Quality Index[37]	X	X	X	X
	Quality of the Relationship[38]	X	X	X	X
Caregiver's sense of competence	Short Sense of Competence Questionnaire[39]	X	X	X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3.

Table 2. Secondary outcomes

	Variable/Instrument		T1	T2	T3	T4
Social reliance	Inventory for Social Reliance[40]		X	X	X	X
Subjective health	Cognitive complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience cognitive complaints?'	X			
		Self-made item: 'In the previous month, have you experienced cognitive complaints?'	X	X	X	X
	Depressive complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience depressive complaints?'	X			
		Self-made item: 'In the previous month, have you experienced depressive complaints?'	X	X	X	X
	Anxiety complaints	Self-made item: 'Before the dementia of your spouse/friend/relative, did you experience anxiety complaints?'	X			
		Self-made item: 'In the previous month, have you experienced anxiety complaints?'	X	X	X	X
Objective health	Number of hospital admissions		X	X	X	X
	Number of hospital visits		X	X	X	X
	Number of GP visits		X	X	X	X
Life events	Self-made item concerning the presence and impact of a positive of negative life event: 'Last month, did something happen in your life which had a major impact on you? This may be something either pleasant or sad'		X	X	X	X
Quality of life	Self-made item concerning the quality of life of the caregivers: 'How would you rate your quality of life on this point in your life?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good)		X	X	X	X
Quality of sleep	Self-made item about the quality of sleep: 'Before the dementia of your spouse/friend/relative, how would you have rated your quality of sleep?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good).		X			
	Self-made item about the quality of sleep: 'How would you have rated your quality of sleep on this point in your life?' The subjects answers by putting an X on a line ranging from 0 (very bad) to 100 (very good).		X	X	X	X
Health and living situation patient	Self-made item concerning the progression of the dementia of the patient: 'How is he or she doing compared to the time of the last interview?' The possible answers are better, the same or worse, than the last interview.			X	X	X
	Self-made item concerning the living situation of the patient: 'Has something changed in the living situation of the patient since the last interview?'			X	X	X
	Self-made item about the concerns of the caregivers about the dementia of the patient: 'Do you have any new concerns about the dementia since the last interview?'			X	X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3.

Possible determinants/confounders

A wide range of possible determinants/confounders (factors in the prediction model and/or covariates) are additionally taken into account, based on what is currently known from the literature about caregivers. These include: sociodemographic variables, medicine use of both caregivers and the people with dementia they care for, and clinical variables regarding the dementia such as the type and time since diagnosis. These data rely on self-report of the informal caregiver. Finally, a couple of qualitative variables are also assessed, e.g. subjective experiences with the simulator (for the intervention group only). Table 3 lists the specific variables assessed and instruments used.

Table 3. Possible determinants/confounders

	Variable/Instrument	T1	T2	T3	T4
Sociodemographic and clinical variables of the caregivers					
Age, gender, education, employment status		X			
Medicine use		X			
Presence and severity of physical disabilities	Self-made question: 'Do you have any physical disabilities and if so, to what extent do these interfere with caregiving?'	X			
Presence and severity of psychological disabilities	Self-made question: 'Do you have any psychological disabilities and if so, to what extent do these interfere with caregiving?'	X			
Variables concerning caregiving	Relationship with the patient with dementia (spouse/daughter/son/something else)	X			
	Distance to the patient (shares household/walking distance/in the same city/in a different city)	X			
	Days providing care a week	X			
	Hours providing care a week	X			
	Years since first time providing care for this patient	X			
	Support of professionals (e.g. housekeeper, case-manager)	X			
	Perceived support of friends or family	X			
Clinical variables of the patient with dementia					
Diagnosis	Alzheimer's disease/Vascular dementia/Parkinson's Disease Dementia/Frontotemporal Dementia/other/unknown	X			
Time since diagnosis (in years)		X			
Medicine use		X			
Comorbidities	Physical comorbidities	X			
	Psychological comorbidities	X			
Support of professional (e.g. physiotherapist)		X			
Self-made items regarding the subjective effectivity of the training*					
'Does the simulator give an accurate reflection of what a demented person goes through?'			X	X	X
'Did the simulator meet your expectations?'			X	X	X
'Do you think the simulator is useful?'			X	X	X
'Did you feel supported by the experiences and stories of the other participants in the group meeting?'			X	X	X
'Did the group meeting meet your expectations?'			X	X	X
'Do you think the group meeting is useful?'			X	X	X
'Did the whole training (simulator and group meeting together) had a personal impact on you?'			X	X	X
'Do you think that the whole training helps you to be a more effective caregiver?'			X	X	X
'Do you think the whole training has helped you to understand your spouse/relative/friend?'			X	X	X
'Do you think that you are better prepared for what is going to happen in the future?'			X	X	X
'Are you surer of your qualities because of the training?'			X	X	X
'Did you learn anything from the training? And if yes, what?'			X	X	X
'Do you do anything different in caring because of the training? And if yes, what?			X	X	X
'Do you think the training missed anything? And if yes, what?'				X	X

Note. T1: 1 week before the simulator training; T2: 1 week after the training; T3: 2.5 months after the training, T4: 12 months after T3. *: Questions for the intervention group only.

Planned statistical analyses

SPSS Statistics 22 will be used for the statistical analyses. Parametric and non-parametric tests will be used to determine if the 2 groups are comparable at baseline on 4 variables, 3 caregiver variables (gender, age and level of education) and 1 person with dementia variable (time since diagnosis). Variables that differ will be used as covariates in the subsequent analyses.

Cross-sectional analyses will be used to evaluate group differences at each of the individual time points (T2-T4) and include $\chi 2$ for categorical variables, the Mann-Whitney U test for ordinal data, and the Student t test or multivariate analysis of variance ((M)AN(C)OVA) for continuous dependent variables. Differences across the time points will be analyzed using multilevel analysis, which allows inclusion of all

available data (i.e. also those from participants with missing data).
The predictive value of the determinants for the primary and secondary outcome measures at T2, T3, and T4 will be determined using multivariate regression analysis (2 time points) or multilevel analysis (> 2 time points). Potential predictors are defined as variables with at least a marginally significant association ($p < .10$) with the outcome. Only these variables will be included in the subsequent analyses to determine the most important predictors. Effects with a 2-tailed $p < .05$ are considered statistically significant. Missing data will be imputed where possible. We will use the Bonferroni correction to correct for multiple comparisons.
A prediction model will be developed to define the most valuable variables for the effectivity of this intervention. Possible predictors are age, gender, relationship with the patient and hours of care.
The qualitative questions in the interviews will be analyzed using descriptive statistics and frequencies.

Sample size and power calculation

The sample size needed is calculated with G*Power, based on the main research question: does the simulator training increase the empathy of informal caregivers? Based on an alpha level of .05 and a power of .80, 64 participants per group are needed to be able to detect a medium difference ($d = 0.5$) between the groups. We expect about 10% drop-out during the 1-year follow-up period due to mortality of the caregivers or the person the caregivers care for, or due to refusal to continue participation. Therefore, we aim to include at least 71 participants in each group; 2*71 = 142 participants in total.

ETHICS AND DISSEMINATION

Ethical considerations

This study is non-invasive and imposes no risk on either the participating caregivers or the people with dementia. This protocol has been approved by the psychological ethical committees of both the Tilburg School of Social and Behavioral Sciences, Tilburg University and De Wever (a care organization for eldercare) in Tilburg, the Netherlands. Written informed consent is obtained from all participants, in accordance with the 'Helsinki Declaration' (Seoul Revision, 2008). The data is stored anonymously and only the primary researchers (LHJ, REM, and MMS) have access to the data. This study has been registered by The Dutch National Trial Register (NTR), number (TC): NTR5856. There is a mismatch in the dates between the start of the study (see Figure 2; July 2014) and the registry date (1st of December 2015). This is because the Into D'mentia simulator was available for 5 weeks in July 2014 for free. At that time it was not certain we could continue the study due to lack of funding. The inclusion of the control group started later when financial support was obtained. The study was registered after this financial support was received, with the corresponding date.

Dissemination

The results obtained will be disseminated to the scientific and general public by publication in national and international (peer-reviewed) scientific and professional journals, as well as by presentations at conferences and meetings with professionals dealing with (informal caregivers of people with) dementia. First, a manuscript with the results of the primary study outcome (empathy) will be published in a peer-reviewed journal. Separate manuscripts will be written on the secondary research outcomes, and these will also be submitted for publication in peer-reviewed journals. The data will not be made public, assuring the study participants' privacy. Requests for data sharing will be considered on an individual basis, for appropriate research purposes only, after completion of the trial, and after publication of the primary manuscript.

DISCUSSION

This is the first study in which the effectivity of a mixed virtual reality dementia simulator is extensively tested in caregivers in a controlled trial. While multiple interventions for caregivers have been designed and tested[42], this is the first dementia simulator in which caregivers actually experience what it is like to have dementia, not only on a functional level, but also emotionally and socially. The focus on experience-based learning makes this intervention very practical.

Strong elements of this study are its longitudinal prospective design with multiple assessments. This is a useful addition to the existing effect studies into interventions for caregivers, which usually apply pre-post designs which makes it impossible to know if these interventions work in the longer term. In addition, we include both quantitative (questionnaires) and qualitative (semi-structured interviews) measurements. We are aware that there are many variables, but we feel that it is necessary to take them all into account because many factors are involved in caregiver burden and need to be considered in any attempt to ultimately figure out which are important. Also, a control group is included which was not always the case in previous intervention studies with caregivers. The control group makes it possible to attribute the findings to the intervention, instead of to other variables such as elapsed time. A potential limitation is that due to practical reasons the participants were not randomized. The simulator was available for free for 5 weeks only (after which it was again made available for a financial compensation), in which we deemed it impossible to include enough caregivers for both the intervention and control group. Instead, the groups are recruited consecutively and we aim to statistically control for differing variables using covariates. These practical reasons were mainly of a financial nature; the intervention is freely available for the public at a cost.
The recruitment of the control group took longer than the recruitment of the intervention group, see Figure 2. This is partly due to the fact that our existing networks were depleted once we started the recruitment of the control group, so new networks had to be formed. Another potential reason was that these (control) participants may have been less eager to participate because they had to wait until the end of the study for their 'reward' (the group meeting).

In conclusion, we hope that this study will determine how effective (or not) the Into D'mentia training is on a variety of variables including empathy and caregiver burden. Furthermore, we believe that it has the potential to contribute to existing knowledge about caregivers. The dementia simulator is expected to be specifically effective in enhancing the quality of life of both caregivers and the people with dementia they care for by helping caregivers understand dementia better in a more personal way.

More informal caregivers than ever before are involved in the care for a family member or friend living with dementia. Helping them in their task should be a priority in health care services around the world. At the moment the Into D'mentia training is too expensive for many individual caregivers (the training costs €240,- per person). If it proves to be effective (on one or more outcomes) the next step would be to do a cost-effectiveness analyses and get it implemented into standard care, making it available for all caregivers and also for care professionals. The ultimate goal is to assist caregivers in the best possible way in their task of caring for their loved ones with dementia, a task most come unprepared to and a task that no one asks for.

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Contributors
LHJ, REM, BWJMJ, JR, RMD, and MMS contributed to study concept, planning and data acquisition, LHJ, REM and MMS will contribute to the statistical analyses, publication and dissemination of findings. LHJ wrote the first manuscript, all other authors provided critical feedback during the manuscript development and approved of the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing Interests
The authors declare that they have no competing interests.

Ethics approval
Approval for this study was provided by the psychological ethical committees of both the Tilburg School of Social and Behavioral Sciences, Tilburg University (number EC-2015.25) and De Wever (a care organisation for eldercare) in Tilburg, the Netherlands. Written consent is obtained from all participants.

Data sharing statement
Data are sensitive and the first priority in sharing data will be protection of study participants' privacy. Therefore, this will not be a public use dataset. The authors will consider requests for data sharing on an individual basis, for appropriate research purposes, after publication of the major findings of the study.

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PLACEMENT FIGURE 1

PLACEMENT FIGURE 2

Figure 1. The simulator's goals

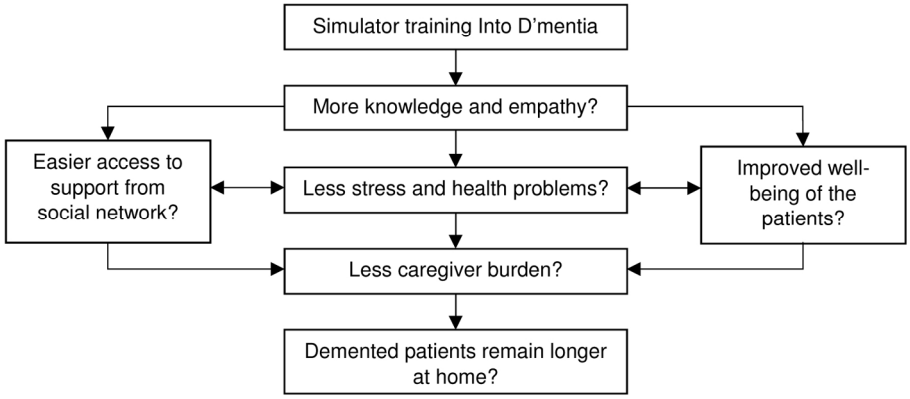

Figure 1. The simulator's goals

155x71mm (300 x 300 DPI)

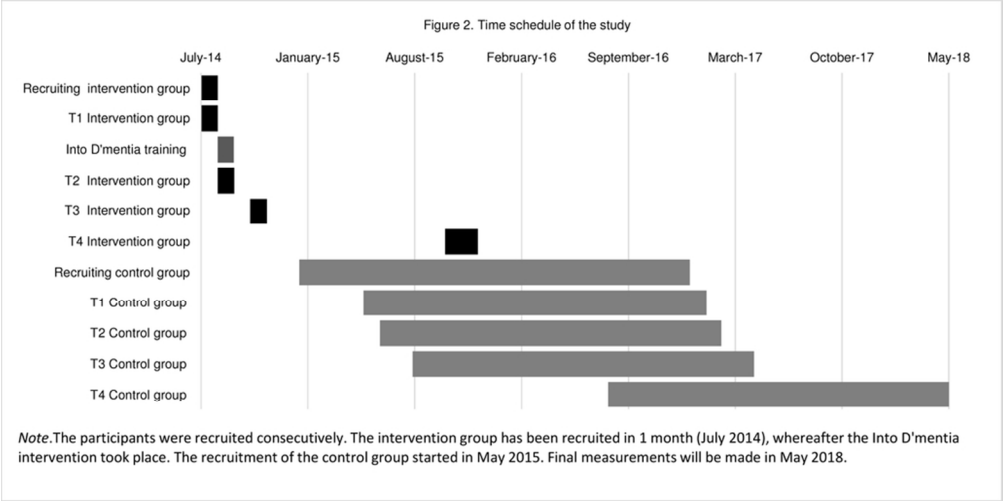

Figure 2. Time schedule of the study

87x43mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	-1 (title page)	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	3	
Methods				
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-10	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	10	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-9	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-9	
Bias	9	Describe any efforts to address potential sources of bias	9-11	
Study size	10	Explain how the study size was arrived at	10	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9-10
		(*c*) Explain how missing data were addressed	9-10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9-10
		(*e*) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	NA
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.