

Neuropsychiatric symptoms in dementia

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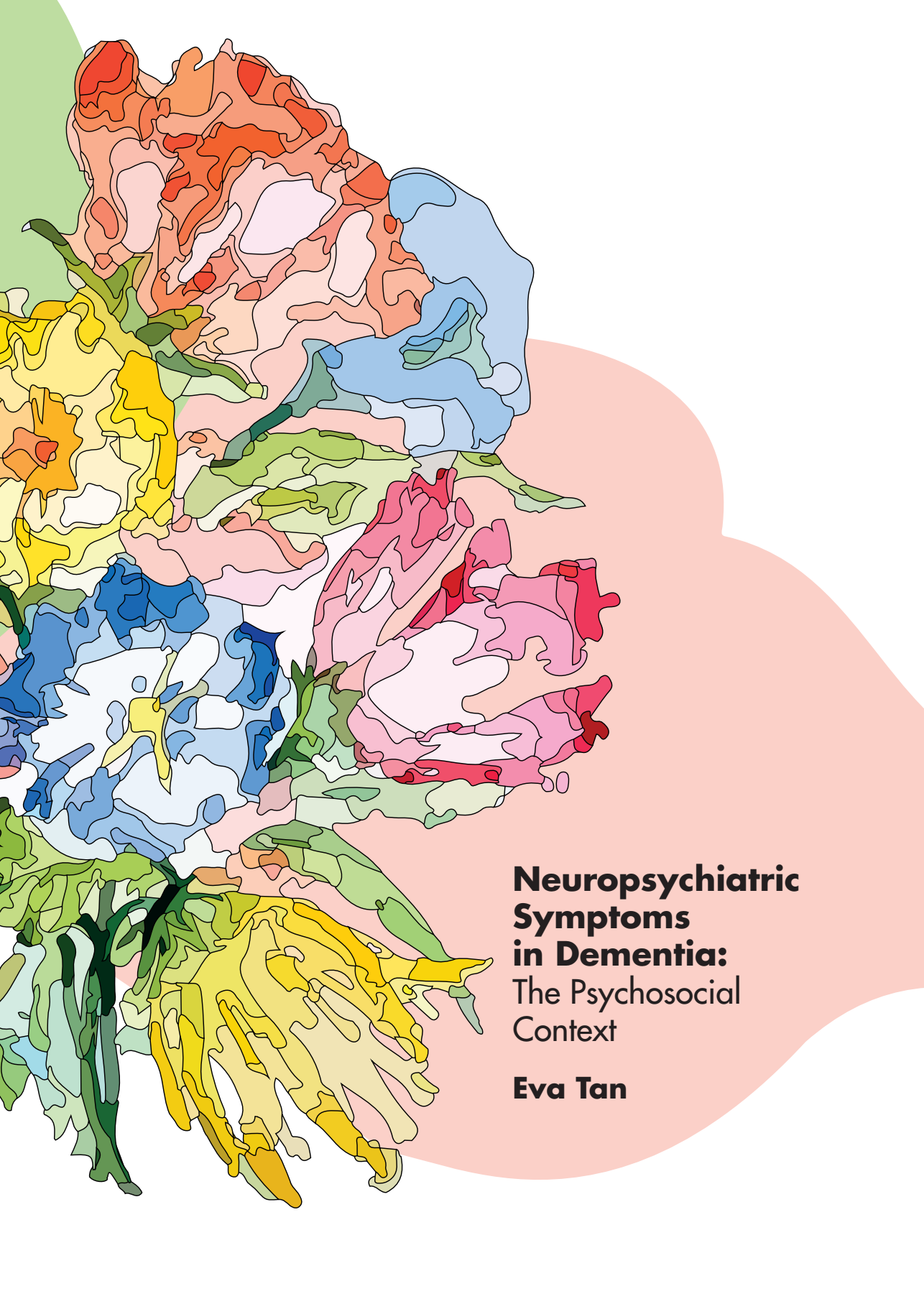
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**Neuropsychiatric
Symptoms
in Dementia:**
The Psychosocial
Context

Eva Tan

NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA: THE PSYCHOSOCIAL CONTEXT

Eva Yu Lin Tan

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Neuropsychiatric Symptoms in Dementia: The Psychosocial Context

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ter verkrijging van de graad van doctor aan de Universiteit
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CHAPTER 1

GENERAL INTRODUCTION

BACKGROUND

Dementia is a syndrome characterized by the deterioration of cognitive functions. Processes like planning, memory, orientation, language and behaviour may be affected. The deterioration will lead to interference with the ability to perform everyday activities.¹ As the population grows older the prevalence of dementia increases. The worldwide prevalence of dementia is an estimated 50 million people, which will expand to approximately 82 million in 2030.² Mild cognitive impairment (MCI) is seen as a transitional state between normal cognitive functioning and dementia.³ It applies to persons who neither have normal cognitive functioning nor dementia and who have a preserved ability to perform everyday activities.³ The prevalence of MCI is estimated between 16% and 20% in persons of 60 years and older.⁴ MCI is seen as a risk state for dementia, but not all persons with MCI will eventually develop dementia.⁵

The impact of MCI and dementia on affected persons, their family and society is enormous. After receiving a diagnosis of MCI the person may be worried or sad, afraid because of the uncertain prognosis and afraid to become dependent.⁶ The loved ones of this person may have the same fears. Furthermore, behavioural changes or neuropsychiatric symptoms (NPS) may arise and relationships may change. In case an MCI progresses to dementia more problems may be experienced. The person with dementia becomes more and more dependent on his or her caregiver, NPS may arise or worsen, relationships can come under pressure and the caregiver may experience higher levels of burden.⁷ Due to these and other factors, quality of life can be seriously affected in persons with dementia⁸, but also in their caregivers.⁹ The deterioration in dementia may eventually lead to nursing home admission. Nursing home admission is often accompanied with grief, because of leaving the familiar environment behind and becoming dependent on a nursing team.

Neuropsychiatric symptoms play a major role in MCI and all stages of dementia, and include apathy, anxiety, depressive symptoms, psychosis, agitation, sleep disturbances, and appetitive changes. Approximately 80-90% of the people with dementia show NPS at some moment during the course of their disease.¹⁰ In MCI the prevalence of NPS is between 35-80%, depending on the population studied.^{11,12} NPS may have several negative effects for the person with dementia resulting in a loss of quality of life.^{13,14} NPS also have a big impact on the family caregivers of the persons with dementia and may lead to negative health effects in the family caregiver.¹⁵ Moreover, NPS are important determinants for nursing home admission, and in this setting NPS may also cause several negative effects for the persons with dementia and for the nursing team.¹⁶

Taken together, NPS and the psychosocial context are of paramount importance during all stages of MCI and dementia. This aim of this thesis is to gain more insight into the associations between NPS, the psychosocial context and the different stages of MCI and dementia.

NEUROPSYCHIATRIC SYMPTOMS IN MILD COGNITIVE IMPAIRMENT

In MCI, the most common neuropsychiatric symptoms include depression, apathy, irritability, anxiety, agitation, and sleeping problems.¹¹ Depressive symptoms are reported most frequently, and occur at very high rates of 40% to 50% depending on the studied population.¹² Some studies suggest that depressive symptoms predict progression from MCI to dementia.¹⁷ Other neuropsychiatric symptoms, like apathy and anxiety, are also linked with accelerated cognitive decline.¹² There are several hypotheses about possible mechanisms between NPS, MCI and the progression to dementia, such as: NPS might be a psychological reaction to unmet needs and/or the awareness of cognitive difficulties; NPS and MCI/dementia may have the same risk factors and therefore co-occur; NPS may be a true risk factor or accelerator for dementia; or, NPS may arise from changes in the brain due to neurodegeneration.^{12,18} A better understanding about the association between NPS and the course of MCI is important, because it could help us in predicting if a person with MCI will develop dementia or not. This will enable persons with MCI and their loved ones to better anticipate their future.

In addition to the potentially important role that NPS have in the progression from MCI to dementia, it is also important to gain insight into the impact of NPS in MCI on the affected persons and their loved ones. NPS in MCI have an important impact on the quality of life of the affected person, especially mood related symptoms.¹⁹ NPS may also have an impact on the wellbeing of their loved ones, like spouses or children.²⁰ However, more research is needed to better understand the association between NPS and the quality of life of the family caregiver in MCI.

Vignette Mrs. V

Mrs. V, a 72-year-old married woman with a history of a mild depressive episode a few years ago, was referred by the general practitioner to an old-age psychiatry clinic because of symptoms of anxiety. During her first appointment in the out-patient department, a clinical interview, a cognitive screening and a physical examination took place. Mrs. V., a friendly woman who looked very vital, was accompanied by her husband. She explained that she suffered a lot from insecurity, while she never lacked confidence in the past. She used to be independent, but now her husband had to accompany her with almost everything. She felt sad about the situation, but she could enjoy activities such as making a walk and playing with her grandchildren. Her husband told the team he was a bit worried about her cognitive functioning. The physical examination revealed no major issues. During the assessment of the Mini Mental State Examination (MMSE) Mrs. V got nervous and achieved a score of 16/30. In the weeks thereafter she got an MRI and an extensive neuropsychological assessment, and

eventually a mild Alzheimer dementia (CDR 1) was diagnosed.

The team was concerned that she would develop NPS with her dementia, given her insecurity and psychiatric history. That was why they asked her to visit the clinic once a month for evaluation of possible problems. In these appointments, fortunately, it seemed that both Mrs. V. as well as her husband were quite capable in accepting the diagnosis. Her husband assisted her in some tasks, but also stimulated her to do some activities herself while coaching her, for example with cooking (something she always loved doing). In doing these tasks she was getting a bit nervous sometimes, but her husband was very good in staying calm and patient, causing her nervousity to fade away. Although sometimes concerned about the future, the team saw an optimistic, loving couple with an open communication. After a year Mrs. V. did not suffer from any relevant neuropsychiatric symptoms and no formal care was needed.

NPS AND PERSONS WITH DEMENTIA LIVING AT HOME

NPS could be a first sign of dementia.¹⁷ The frequency and severity of NPS may increase with cognitive decline^{21,22} with a peak in prevalence in moderate stages of dementia.²³ The mild depressive episode that *Mrs. V* suffered from a few years ago might have been a first sign of the dementia she developed in the years thereafter. Indeed, a systematic review found that depression before a diagnosis of dementia was associated with subsequent cognitive decline, whereas symptoms of hyperactivity, including aggression and agitation, were associated with more severe cognitive impairment.²⁴

Thus, the frequency and severity of NPS are partly associated with the stage of dementia, but they are also associated with other patient-related factors such as age and comorbidity.²⁵ In addition, also environment-related factors can explain differences in prevalence in NPS between persons with dementia.²⁶ Throughout the different stages of dementia, the physical and psychosocial environment could play an important role; for example, the way different kind of caregivers cope with the challenges of dementia. These environment-related factors are important since they may be modifiable and could be a starting point for non-pharmacological interventions reducing NPS.

In persons with dementia living at home, the interaction with the family caregiver may influence the behaviour of the person with dementia.²⁷ In the case of *Mrs. V* her husband is very supportive and their relationship remained very good. He assisted and coached her in some tasks but let her have the lead. This ‘supportive’ caregiver strategy might result in less NPS.²⁸ Methods that have been developed to capture this interpersonal interaction are for example expressed emotion (EE)²⁹ and measurements of the relationship quality.³⁰ A systematic review found an association between factors associated with relationship quality and global challenging behaviour, but the evidence was weak²⁷ and more research is needed.

Vignette Mr. B

An old-age psychiatrist and an old-age psychologist are asked for a consultation of a patient with dementia in a nursing home (Mr. B), because the nursing team suspects an autism spectrum disorder and they would like to see that diagnosis confirmed. The psychiatrist and psychologist visit the patient, interview the nursing team including the head of the unit and schedule an appointment with the family of the patient. While visiting the nursing home unit they notice the tranquility on the unit, the warm involvement of the nursing team and a homelike atmosphere. They also realize they never visited this nursing home unit before. They wonder if there is an association between the friendly atmosphere on the unit and the low prevalence of behavioral problems. Out of interest, they discuss this with some of the nurses and discover that the nurses love their job, moreover, they feel in control of their job. They are able to organize their work in a way they think is right, but also feel supported by the head of the unit when needed. Furthermore, they explain that they get time for team meetings to discuss quality of care and talk about possible developments and improvements.

NPS AND PERSONS WITH DEMENTIA LIVING IN A NURSING HOME

In nursing homes, the interactions between the person with dementia and the psychosocial environment could also be associated with the emergence of NPS. This includes the direct interaction between the person with dementia and the professional caregivers³¹, but also the atmosphere of a nursing home unit.³² In the example of the nursing team of *Mr. B* the question is whether there is an association between the friendly atmosphere and the low prevalence of NPS on the unit. In this team the nurses get along well, they do not seem stressed and they feel supported by their supervisor. There are also examples where the opposite seems to be happening: overworked teams with a lot of irritation between the team members and a high demand to ‘do something about’ the behavioral problems in their nursing home residents. In these situations, the nurses may experience a high work load, a lack of control and not enough support.

In other words, also the way professional caregivers experience their job may be related to the prevalence and severity of NPS. These experiences can be translated into job characteristics described by Karasek et al. in the Job Demands-Control-Support model.³³ An indication of a possible influence of job characteristics on NPS is that nursing staff distress is associated with psychotropic drug use in nursing home residents.³⁴

Extensive research has been done on the influence of patient-related factors and physical environmental factors on NPS in nursing home residents with dementia^{25,26,35}, but less research had been done on the association with psychosocial environmental factors such as the job characteristics of the nursing team.

THE PSYCHOSOCIAL CONTEXT AND NEUROPSYCHIATRIC SYMPTOMS

As described above, multiple factors may play a role in NPS in MCI and dementia. Next to disease-related or biological factors, also different aspect of the psychosocial context may be important. Therefore, the 'biopsychosocial model of health'³⁶ could be a useful framework to understand the associations between the psychosocial context and NPS in MCI and dementia. The biological, psychological and social factors of this framework are thought to be dynamic, because that they can change over time during the course of the disease.³⁷ Especially the psychosocial or interpersonal factors are complex and different levels of interaction may exist. Moreover, the psychosocial factors are related to the setting or context where the concerning person lives. In MCI and dementia this context may change during the course of the disease. This underlines the importance of studying the associations between the psychosocial context and NPS in all the different stages of MCI and dementia.

OUTLINE OF THE THESIS

This primary objective of this thesis is to gain more insight into the associations between NPS, the psychosocial context and the different stages of MCI and dementia. Chapter 2 and chapter 3 represent the earlier stages: MCI and conversion to dementia. Chapter 4 and 5 focus on persons with dementia and their family caregivers living at home, while chapter 6 describes a study in nursing homes.

In chapter 2 the question is asked whether depressive symptoms influence the conversion from MCI to dementia, and whether there are differences between a community and a clinical setting. This question is answered by means of a systematic review and a comparative meta-analysis of clinical and community-based studies.

In Chapter 3 the aim was to analyse the quality of life of caregivers in MCI and its possible determinants, including NPS. Also, a comparison with dementia is made. This is done by a cross-sectional study in two multicentre studies.

Chapter 4 presents a longitudinal study in which a person-centered approach with growth mixture modelling is used to analyse trajectories of relationship quality in persons with dementia living at home and their family carers. The possible influence on relationship quality levels and trajectories of multiple variables, including neuropsychiatric symptoms, is also examined.

Chapter 5 describes a longitudinal study to examine the interaction of caregiver expressed emotions (EE) and NPS in persons with dementia living at home. In addition, factors associated with EE are explored, a possible association between EE and institutionalization rate is examined and the impact of EE on caregiver functioning is studied.

In Chapter 6 the influence of job characteristics of the nursing team on agitation in residents with dementia is analysed. This is done in a cross-sectional study in 22 dementia care units in 3 nursing home organizations in the South of the Netherlands.

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CHAPTER 2

DEPRESSIVE SYMPTOMS IN MILD COGNITIVE IMPAIRMENT AND THE RISK OF DEMENTIA: A SYSTEMATIC REVIEW AND COMPARATIVE META-ANALYSIS OF CLINICAL AND COMMUNITY-BASED STUDIES

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ABSTRACT

Background

Affective symptoms are considered a risk factor or prodromal symptom for dementia. Recent reviews indicate that depressive symptoms predict progression from mild cognitive impairment (MCI) to dementia, but results need to be further explored.

Objective

To investigate the effect of depressive symptoms on the development of dementia in people with MCI, and explore potential sources of between-study variability, including study setting by a systematic review and meta-analysis.

Methods

Databases were searched for prospective studies defining people with MCI at baseline, investigating dementia at follow-up and giving information about depressive symptoms. Two authors independently extracted data from the studies and rated the methodological quality. Meta-analyses were conducted using random-effect models to yield pooled risk ratios (RR). Meta-regression analyses tested differences between clinical and community-based studies and other sources of heterogeneity.

Results

Thirty-five studies, representing 14,158 individuals with MCI, were included in the meta-analysis. Depressive symptoms in MCI predicted dementia in 15 community-based studies (RR = 1.69, 95% CI 1.49–1.93, I^2 = 0.0%), but not in 20 clinical studies (RR = 1.02, 95% CI 0.92–1.14, I^2 = 73.0%). Further investigation of this effect showed that the mean age of community-based studies was significantly higher than of clinical studies but neither this nor other study characteristics explained variability in study outcomes.

Conclusions

Depressive symptoms are associated with an increased risk of conversion from MCI to dementia in community-based studies. In contrast, evidence in clinical populations was insufficient with high heterogeneity.

Keywords

Dementia, depression, depressive symptoms, meta-analysis, mild cognitive impairment, risk factors, systematic review

INTRODUCTION

Mild cognitive impairment (MCI) is a well-known risk state for developing dementia, but the heterogeneity in underlying etiologies leading to cognitive impairment causes diversity in outcome. Importantly, not all individuals with MCI will develop dementia; a longitudinal study found that less than half of the individuals with amnesic MCI will develop dementia within ten years.¹ It is important to gain insight into easily-accessible factors that predict who will develop dementia and who will not. This might indicate potential for secondary prevention or, alternatively, lead to an earlier and more accurate diagnosis, give opportunities to start care and treatment timely, and to enable patients and their families to better anticipate their future.

Affective symptoms are considered a major risk factor or prodromal symptom for dementia in the general population.^{2–4} However, their predictive value in persons with MCI is unknown as current results are conflicting. A recent review and meta-analysis of a broad range of potentially modifiable predictors of dementia in MCI found that there is evidence that depressive symptoms predict progression from MCI to dementia in community-based studies, but not in clinical studies.⁵ However, the study was not specified for depressive symptoms, and hence only 13 studies were included and the associations were not further explored. Additionally, another recent review and meta-analysis found evidence that depressive symptoms increase the risk of progression from MCI to dementia, but heterogeneity was very high and not further explored.⁶

The aim of this study is to systematically review the current evidence and perform a meta-analysis to investigate the effect of depressive symptoms on the development of dementia in persons with MCI. In addition, we investigate study characteristics that may explain the variability in study outcomes, especially differences between community-based and clinical studies.

METHODS

This study adhered to the PRISMA statement: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.⁷

Search strategy

We searched the PubMed, PsycINFO, EMBASE, and CINAHL databases for relevant studies published until March 31, 2018. The following search terms were used: ‘human’ and ‘depression’, ‘anxiety’, ‘apathy’, ‘aggression’, ‘irritability’, ‘affective’, ‘mood’, ‘behavioral’, ‘neuropsychiatric’, or ‘behavioral and psychological symptoms of dementia’ and ‘mild cognitive impairment’, ‘MCI’, ‘amnesic’, ‘amnesic syndrome’, ‘memory impairment’, ‘mild cognitive decline’, ‘age-associated cognitive decline’, ‘AACD’, ‘age-

associated memory impairment', 'AAMI', 'cognitive impairment no dementia', 'CIND', 'memory clinic', 'memory disorders clinic', 'dementia clinic' or 'memory disorder clinic' and 'follow-up studies', 'follow up studies', 'follow-up study', 'follow up study', 'follow up', or 'follow-up'. Neuropsychiatric symptoms such as anxiety and apathy were included in the search because of possible overlap with depressive symptoms and potential that associations were reported in sub-analyses. No search limits were applied.

Titles and abstracts of the retrieved studies were reviewed using the criteria specified below. Additionally, references of relevant publications were searched to identify additional studies.

Study selection

Studies were selected for further analysis if they fulfilled the following inclusion criteria: 1) prospective study; 2) defining individuals with MCI at baseline; 3) a diagnosis of dementia at follow-up according to any of the following criteria: Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) (American Psychiatric Association, 1994), DSM 3rd Revised Edition (DSMIII-R) (American Psychiatric Association, 1987), the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organization, 1993), National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA); 4) Available information on depressive symptoms or depression at baseline; and 5) A study cohort of 50 or more individuals.

We included all studies that defined MCI as subjective and/or objective cognitive impairment, without fulfilling dementia criteria. We included all subtypes of MCI, except for studies focusing on MCI in Parkinson's disease.

Data extraction

Two authors independently extracted the data from the studies. When available, we extracted both the number of individuals with and without baseline depression or depressive symptoms (dichotomous variable) of converters and non-converters to dementia. We also extracted the reported risk measure including the 95% confidence interval. In addition, the following study characteristics were extracted: setting (clinical studies versus community-based studies), inclusion and exclusion criteria (specifically exclusion of a baseline major depressive disorder), MCI definition, measurement of depression, subject characteristics (e.g., gender, age, Mini-Mental State Examination (MMSE), education) and number of converters to dementia. Concerning the characteristic 'setting' the studies were divided into two types of studies: 1) Clinical studies: studies performed in a clinical setting (e.g., memory clinic); and 2) Community-based studies: studies performed in the general population.

In case the two authors disagreed, a third author reviewed the paper and consensus was reached. In case of incomplete data, authors were contacted and asked to complete

or specify the data.

Assessment of methodological quality

To assess methodological quality, two reviewers rated each study according to a 19 items scale derived from a published method.⁸ For the specific items, see Supplementary Table 1. In case of discrepancies between the reviewers, a third reviewer was asked to review and score to reach consensus. A median split and a split into tertiles of the total quality score classified studies into those with low, medium or high risk of bias.

Statistical analysis

Analyses were performed using STATA/MP version 12.1 for MacOSX (StataCorp, Texas). Statistical significance was set at $p < 0.05$ in two-sided tests. The main outcome measure was the pooled risk ratio (RR) from random-effect models.

Unadjusted RR and standard errors (SE) were calculated directly from raw tables. For four studies raw data were not available and the reported risk measure was used. These risk measures were log-transformed and standard errors were calculated from the 95% confidence interval (CI). For two of these studies, only a hazard ratio (HR) was reported, but it was considered equivalent to the RR.

The amount of heterogeneity was calculated with the DerSimonian and Laird method, which is a method to estimate the variance between studies. I^2 denotes the proportion of the observed variance between studies that reflects real differences rather than chance and was used next to the Q-statistic to assess heterogeneity. We performed meta-regression analyses to investigate possible sources of heterogeneity, i.e., sampling method (clinical versus community-based setting), baseline mean age of the cohort, baseline MMSE score, conversion rate, publication year, depression versus depressive symptoms, and whether studies used major depression as an exclusion criterion. Analyses were performed 1-by-1 for all variables, analyses were first performed on all studies and then for community and clinical studies separately. Publication bias was investigated using Egger's regression test and a visual inspection of the funnel plot.

RESULTS

Search results

A total of 5,470 publications were reviewed on title and abstract, of which 208 publications were selected for further scrutiny (Fig. 1). Additionally, 20 publications were retrieved through references. Of these 228 papers, 98 were excluded due to overlap in used literature databases. Additionally, from the remaining 130 papers, 8 were posters or correspondence letters, 18 gave no or unclear information about baseline depressive symptoms, 20 referred to the same cohort as another publication, 23 were excluded

because of other reasons, and 26 publications were not included because not enough data were available. Concerning the publications reporting on the same cohort, the publication with the largest sample size was selected, if the sample size was the same then the study with the longest follow-up was selected. There was one exception, concerning the data of the Alzheimer's Disease Neuroimaging Initiative (ADNI); a recent study was selected fitting our research question most properly. Finally, 35 studies were included in the meta-analysis.

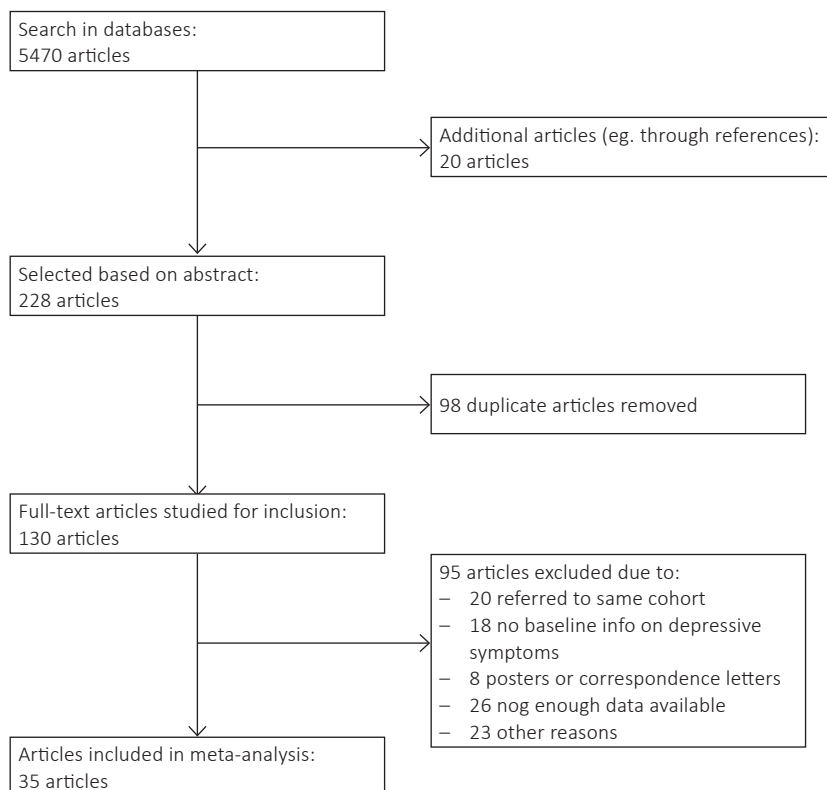


Figure 1. Selection of studies

Study characteristics

In total, the 35 studies (Table 1)^{9–43} included 14,158 individuals with MCI, of whom 7,855 (57.2%) were female (data missing for 1 study³⁵, $n = 429$). Of the 35 studies, fifteen were community-based studies ($n = 6,803$) and twenty ($n = 7,355$) were based on clinical samples. In 23 studies, MCI was defined according to the Petersen criteria⁴⁴ or minor variants thereof. The mean baseline age was 73.7 years (SD 4.2), mean MMSE score was 26.3 (SD 2.0) and mean education was 10.9 years (SD 3.8). In total, 3,509 (27.6%)

MCI individuals showed depression or relevant depressive symptoms at baseline (not specified for 4 studies^{21,35,42,45}, $n = 1,427$), 25.1% in community-based studies, and 32.5% in clinical studies.

In total, 3,208 (22.7%) individuals progressed from MCI to dementia during a mean follow-up period of 3.0 (SD 1.3) years. In 27 studies, it was specified whether the dementia was due to Alzheimer's disease, which was the case in 2,367 of 11,315 (20.9%) individuals.

Meta-analysis

Dementia developed in 1,043 (29.6%) individuals with MCI with depressive symptoms at baseline, compared to 1,833 (21.1%) MCI individuals without depressive symptoms at baseline (raw data missing for 4 studies [10, 16, 26, 40]). The accompanying pooled RR based on data from all 35 studies was 1.19 (95% CI = 1.07–1.32). When the two studies reporting HRs were excluded, the pooled RR was 1.22 (95% CI 1.06–1.41). When the four studies that reported ratios instead of raw data were excluded, the pooled RR was 1.22 (95%CI = 1.06–1.40).

There was significant heterogeneity across studies ($I^2 = 73.6\%$, $p < 0.001$). Since we expected sampling method (clinical versus community-based) to partly explain differences between studies, we conducted meta-analysis stratified by sampling method. In community-based samples, the pooled risk ratio was 1.69 (95%CI = 1.49–1.93), compared to 1.02 (95%CI = 0.92–1.14) in clinical samples (Fig. 2). Additionally, heterogeneity was high in clinical studies ($I^2 = 73.0\%$) but marginal in community-based studies ($I^2 = 0.0\%$).

Exploratory analysis of additional variability in study outcomes

Studies were divided in two age groups: studies with a mean age ≥ 75 years (8 studies, $n = 1927$) and studies with a mean age < 75 years (25 studies, $n = 11087$). The pooled risk ratio for studies with a mean age ≥ 75 years was 1.41 (95%CI = 1.12–1.77) and for studies with a mean age < 75 years 1.16 (95%CI = 0.99–1.37). However, there was a large overlap between the community-based studies and the studies with a mean age ≥ 75 years, with a higher mean age in community-based studies than in clinical studies (76.4 versus 71.8, $p < 0.001$). To understand this effect further, we divided the community-based studies into those with a mean age ≥ 75 years or below. This showed slightly stronger associations in the younger cohorts (RR = 1.71, 95%CI = 1.38–2.14) versus the older cohorts (RR = 1.60, 95%CI = 1.32–1.93). The same analysis could not be performed in the clinical studies because only one of them had a mean age ≥ 75 years.

Table 1. Characteristics of studies included in the meta-analysis

Study	Year	Setting	Sample size	MCI definition	Depression scale	Prevalence depression / depressive symptoms (%)	Mean follow-up (years)	Mean age (years)	Mean education (years)	Mean MMSE	Conversion rate (%)
Tierney ²⁹	1999	Community	125	Symptomatic memory problems, no dementia	GDS-30	22.4	2	72.0	14.0	-	21.6
Visser ²⁸	2002	Community	63	'Minimal dementia'	clinical	11.1	2.3	79.5	7.3	22.5	53.0
Copeland ²⁷	2003	Community	123	CDR = 0.5	interview	43.8	3	72.2	14.9	29.1	20.3
Korf ²⁶	2004	Clinical	71	Petersen (close to)	MADRS	41.3	2.8	62.9	10.2	26.9	49.3
Modrego ²⁴	2004	Clinical	114	Petersen	GDS-30	36.0	3	72.8	-	-	51.7
Robert ^{30 (1)}	2006	Clinical	216	Petersen (close to)	MADRS	19.9	1	71.9	-	27.5	10.2
Teng ²³	2007	Clinical	51	Petersen	NPI	39.2	2.1	72.8	16.6	27.6	23.5
Artero ²²	2008	Community	2879	Petersen, MCI-revised ^a	CES-D	30.8	4	74.6	-	-	6.6
Houde ²⁰	2008	Clinical	60	Petersen	GDS-30	51.7	4.3	74.5	10.5	27.2	60.0
Fellows ^{19 (2)}	2008	Clinical	90	Petersen	GDS-30	57.8	3.3	73.7	10.7	27.5	56.0
Panza ¹⁸	2008	Community	121	Petersen, without SMC as criterion	GDS-30	61.2	3.5	80.6	2.2	21.4	10.8
Robert ^{17 (3)}	2008	Clinical	214	Petersen (close to)	'lack of interest'	22.0	3	71.9	-	27.5	27.2
Devier ^{16 (4)}	2009	Clinical	148	86.5% Petersen (post-hoc)	HAM-D	22.3	3.9	67.1	15.0	27.5	26.4
Edwards ¹⁵	2009	Clinical	521	aMCI, single non-memory MCI, mdMCI	clinical	38.1	1.6	72.8	13.0	26.3	67.0
Vicini Chilovi ¹⁴	2009	Clinical	124	Petersen, MCI-revised ^a	GDS-15, NPI	47.6	2	71.3	7.5	26.6	22.6
Velayudhan ¹²	2010	Community	103	Petersen	Cornell, NPI	29.4	4	79.4	10.6	26.3	31.0
Palmer ^{11 (5)}	2010	Clinical	131	Petersen	NPI	34.3	1.4	70.8	-	27.2	15.2
Ramakers ⁴³	2010	Clinical	263	GDS 2-3	HAM-D	51.6	5.4	66.9	-	27.6	34.2
Gallagher ⁴²	2011	Clinical	161	Petersen	BEHAVE-AD	25.5	2.25	73.7	-	25.4	43.0
Caracciolo ⁴¹	2011	Community	160	Petersen + oCIND	'low mood'	36.0	3	-	-	-	31.3
Chan ⁴⁰	2011	Community	321	Petersen	NPI	16.8	2	77.3	3.0	24.3	15.9
Sikkes ³⁹	2011	Clinical	531	'Cognitive complaints'	Differed	10.0	1	69.6	10.0	27.5	13.0
Brodsky ³⁸	2012	Community	319	Petersen	NPI	12.4	2	79.0	11.6	27.6	4.7
Conde-Sala ³²	2012	Clinical	109	EADC	CAMDEX-R	53.8	5	74	-	21.3	39.4
Luck ³⁷	2012	Community	483	Petersen, MCI-revised ^a	GDS-15	13.9	3.7	80.1	-	26.0	24.2
Mauri ^{21 (6)}	2012	Clinical	208	Petersen	GDS-30	41.8	6	73.6	7.5	25.6	68.8
Steenland ³⁶	2012	Clinical	3010	NACC's definition	GDS-15, NPI-Q	35.3	2.5	74	-	27.2	39.0
Richard ³⁵	2013	Community	429	Petersen	CES-D	24.0	5.1	-	-	-	20.9

Table 1. Continued

Study		Setting	Sample size	MCI definition	Depression scale	Prevalence depression / depressive symptoms (%)	Mean follow-up (years)	Mean age (years)	Mean education (years)	Mean MMSE	Conversion rate (%)
Brodsky ³⁴	2014	Clinical	185	Petersen, MCI-revised ^a	NPI	33	3	75.8	-	27.0	28.1
Van der Musselle ^{33 (7)}	2014	Clinical	183	Petersen	CSDD or GDS-30	22.4	3.8	74.9	10.9	26.0	59.6
Pink ³¹	2015	Community	332	Petersen	NPI-Q	25.3	Median: 3	Median: 82.1	Median: 12.0	-	35.2
Makizako ²⁵	2016	Community	732	>25 on MMSE, cognitive impairment, no functional dependency	GDS-15	16.1	2	71.8	11.3	-	4.5
Kida ¹³	2016	Community	276	Cognitive complaints, objective impairment, preserved ADL	GDS-15	23.2	5.2 (incl. controls)	73.1	9.8	-	22.8
Myung ¹⁰	2017	Clinical	961	NIA-AA definition	GDS-15	-	Median: 1.5	Median: 71	Median: 8	Median: 25	29.1
Moon ⁹	2017	Community	337	Petersen	NPI-Q	22.3	1.9	71.8	16.2	28.1	15.4

CAMDEX-R = Cambridge Examination for Mental Disorders of the Elderly – revised, CES-D = Center for Epidemiological Studies Depression scale, CDR = clinical dementia rating scale, CNPI = EADC = European AD Consortium, GDS = Global Deterioration Scale, GDS-15 / GDS-30 = Geriatric Depression Scale, CSDD = Cornell Scale for Depression in Dementia, HAM-D = Hamilton Depression Rating Scale, MADRS = Montgomery – Åsberg Depression Rating Scale, NACC = National Alzheimer's Coordinating Centre, NIA-AA = National Institute of Aging and Alzheimer's Association, NPI = Neuropsychiatric Inventory, SMC = subjective memory complaints.^a Winblad et al. 2004.⁴⁶ Extra information about depression as an exclusion criterion in some of the studies: ⁽¹⁾ MADRS > 20, ⁽²⁾ Yesavage Geriatric depression scale >16 (major depression), ⁽³⁾ MADRS > 20, ⁽⁴⁾ 'Current major affective disorder', ⁽⁵⁾ 'Patients with major depressive disorder if meaningful clinical improvement in cognition accompanying improvement in depression was observed within 6 months of antidepressants treatment initiation', ⁽⁶⁾ GDS-30 > 17, ⁽⁷⁾ CSDD ≥ 22 or GDS-30 ≥ 21, ⁽⁸⁾ GDS-15 ≥ 6

Multivariable meta-regression of all 35 studies suggested that only setting (clinical, community) significantly explained heterogeneity between studies (residual $I^2 = 60.0\%$). In this model, community-based studies reported on average a 1.61-fold higher risk (95%CI = 1.24–2.09) as a function of depression compared with clinical studies. Adding mean age to this model did not substantially change results (RR = 1.58, 95%CI = 1.13–2.22, residual $I^2 = 60.0\%$). Studies with a higher mean age did not convey a higher risk in this model (RR for age = 1.01, 95%CI = 0.97–1.05).

In an attempt to explain the variability in outcome in clinical studies, several meta-regression analyses were conducted (see Supplementary Table 2). Although all articles gave information on depression or depressive symptoms at baseline, in some clinical studies major depressive disorder was an exclusion criterion. There was no significant difference in the risk of progression to dementia in clinical studies with and without major depressive disorder as an exclusion criterion (Coef. 0.12, $p = 0.627$).

Studies also differed in the way depression was defined, with some studies investigating depression according to clinical criteria and others as scoring above the cut-off on continuous symptom scales. Meta-regression analysis did not reveal any significant difference in outcome according to exposure definition (Coef. 0.20, $p = 0.373$). The Geriatric Depression Scale (GDS-15 or GDS-30) was the most commonly used scale ($n = 9$ out of 20 clinical studies) to measure depressive symptoms, but usage of the GDS versus other instruments did not result in a significantly different outcome (Coef. 0.02, $p = 0.927$). We further found no significant effect of other study characteristics: Peterson criteria for MCI (yes, no), clinical diagnosis of depression (yes, no), study quality (tertiles), mean MMSE score, mean follow-up duration, publication year, and conversion rate for explaining heterogeneity in clinical studies. Meta-regression analysis with the characteristic mean education was not possible, due to insufficient and possibly not comparable data.

Small sample effect

Visual inspection of the stratified funnel plots for community and clinical studies, as well as Egger's regression tests for community studies (bias coef. -0.860 , SE 0.542 , $p = 0.137$) and clinical studies (bias coef. -0.675 , SE 0.783 , $p = 0.824$), showed little evidence for small study effects.

Methodological quality

Meta-regression showed that studies with high or low risk of bias did not explain heterogeneity in study outcome. Dividing methodological quality scores into tertiles did not change this.

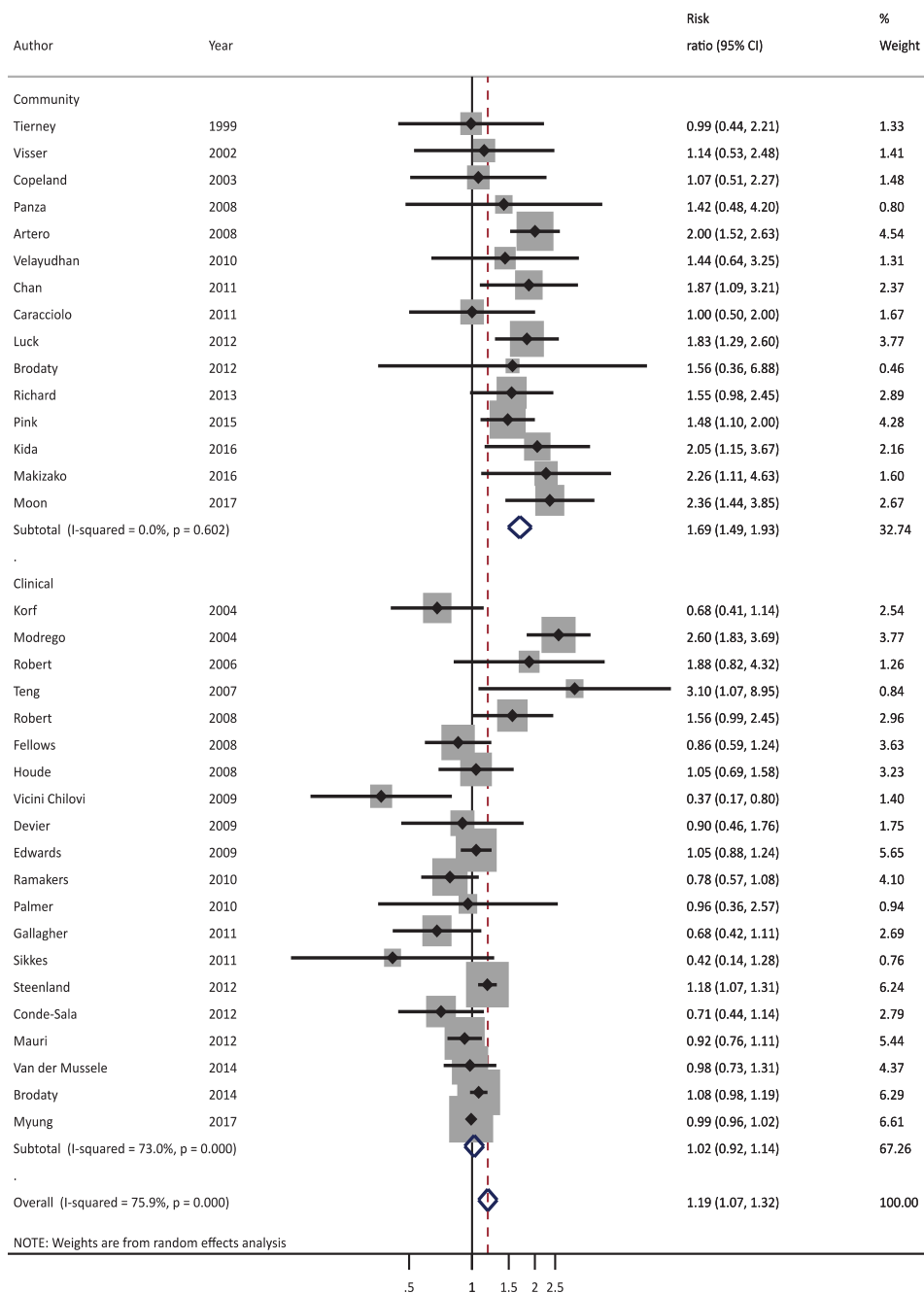


Figure 2. Pooled Risk Ratios for studies grouped by setting

DISCUSSION

In a meta-analysis of 35 studies, representing almost 15,000 individuals with MCI, we found strong and consistent evidence that depressive symptoms predict a higher dementia risk in community-dwelling persons with MCI. The pooled risk ratio suggests a 1.69 times higher risk in depressed people with MCI for conversion to dementia with very low between-study heterogeneity. In contrast, the pooled risk was not increased in clinical cohorts with MCI, and heterogeneity in these studies was high. Other study characteristics did not explain the difference between clinical and community-based studies.

These findings give important insight into the robustness of the association between depression in MCI and risk of dementia conversion. A recent meta-analysis with a smaller total population⁶ found depression to be associated with an increase in the risk but reported high variability in study outcomes. In the current study, an association with depression was only found in the community-based studies, which has also been shown in an earlier study by Cooper et al.⁵ The latter was, however, a smaller study (13 studies on depression compared to 35 in the present one), not focusing on depressive symptoms in particular. Importantly, our meta-regression analyses show that the difference between study settings is not explained by other study characteristics such as mean age, follow-up-duration, definition of MCI, or how depression was assessed.

The results of our study and these two studies also amplify two meta-analyses in cognitively healthy persons: a meta-analysis² studying the risk of dementia in cognitively healthy older adults with late-life depression in community-based prospective cohort studies found that late-life depression is associated with a 1.8-fold increased risk of incident all-cause dementia, and a meta-analysis³ that found that cognitively-healthy persons with a history of major depression are more likely to be diagnosed with Alzheimer's disease later in life than persons without a history of major depression.

In clinical studies we could not find an association between depressive symptoms and the progression from MCI to dementia. A possible explanation is that heterogeneity in clinical studies was very high ($I^2 = 73.0\%$). An exploratory analysis indicated that age partly explains this heterogeneity. Another possible explanation for the heterogeneity might be that there are many different types of memory clinics in and outside hospitals with different populations (e.g., neurology, psychiatry, internal medicine). A study in a clinical population on neurobiological correlates of depressive symptoms in individuals with MCI and subjective memory impairment found that depressive symptoms are common, but not associated with pathological Alzheimer's disease biomarkers.⁴⁵ The authors suggest that in their clinical population depressive symptoms may drive the cognitive symptoms rather than being a mere correlate of neurodegenerative changes. This finding could also explain why some of the clinical studies in this meta-analysis found a negative relation between depressive symptoms and progression from MCI

to dementia. Also, in clinical studies of individuals seeking help, one could expect the symptoms, whether being depressive symptoms or cognitive problems, to be more severe. This could lead to hypothetical subgroups of individuals with MCI with different subsets of symptoms and a different course and outcome. A recent study by Hanfelt et al.⁴⁷ on latent classes of MCI, in a clinical population, indeed found that seven latent classes of MCI differed significantly in clinical outcome. It could be that the heterogeneity in the clinical studies is a reflection of different classes with different outcomes, while in the community studies the homogeneity may indicate fewer classes or a different distribution.

The direction of the relation between depression and dementia in the community-based studies remains unclear. Different hypothesis are plausible and described in the literature, suggesting a causal or corollary effect or favoring reversed-causality.^{48,49} For instance, depressive symptoms may interact with, or provoke, the pathophysiological mechanism(s) of dementia, for example due to a cortisol-hippocampal pathway⁴⁸, resulting in a faster progression from MCI to dementia. Another hypothesis is that the progression from MCI to dementia itself leads to depressive symptoms, for example as an early symptom.⁵⁰ A quite similar hypothesis could be that the awareness of the patient that his or her cognitive functions are failing results in depressive symptoms. A fourth, and often postulated, hypothesis is the vascular depression hypothesis in which depression is associated with an increase in vascular risk factors and therefore an increased incidence of cognitive dysfunction due to cerebral small vessel disease.⁵¹ Indeed, some studies suggest that cerebrovascular factors are the link between depressive symptoms and the progression from MCI to (vascular) dementia.^{35,52} Moreover, the meta-analysis of Diniz et al. found that, in case of late-life depression, the risk of vascular dementia is significantly higher than for Alzheimer's disease. Unfortunately, we were not able to perform a separate analysis focusing on vascular dementia due to insufficient data. Late-life dementia is often due to mixed brain pathologies (i.e., both vascular and Alzheimer's disease factors).⁵³ Since depression has been strongly related to cerebrovascular disease including cerebral small vessel disease⁵⁴, stroke⁵⁵, and vascular dementia², its predictive value for dementia should be higher in populations that comprise more (mixed) vascular pathologies. This might also explain the paralleling effect of age: since the mean age in community studies was higher than in the clinical studies, there may have been more vascular or mixed dementias in the community-studies. Of course, also a combination of these different hypotheses is possible in which different mechanisms operate in different (groups of) individuals (Fig. 3).

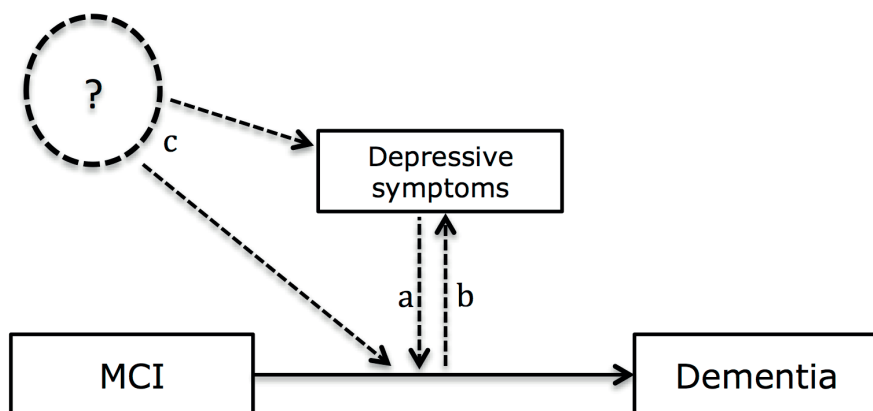


Figure 3. Different hypotheses concerning the direction of relation between depressive symptoms and progression from MCI to dementia:

- a. Depressive symptoms influence the pathophysiological mechanisms of dementia
- b. 1. The progression from MCI to dementia itself leads to depressive symptoms as an early symptom
2. The awareness of failing cognitive functions leads to depressive symptoms
- c. Another factor (e.g. vascular risk factors) leads to progression to dementia and to depressive symptoms

Although the direction of the association between depressive symptoms and dementia in the community studies is unclear, the present study does imply screening of depressive symptoms in MCI. The detection of depressive symptoms may lead to adequate treatment and a better quality of life, and may possibly modify the progression from MCI to dementia.

Strengths of this study are the comprehensive and broad search for the literature review, and the extensive analyses. However, the study has several limitations. First, useful studies may be missing because not all data were available in the published papers and not all authors of previous studies replied to our requests for additional data, for example because the authors were already retired. These studies were mainly studies with an earlier publication year. Furthermore, as noted before, we were able to include 35 studies, instead of the 13 and 18 studies included in earlier meta-analyses.^{5,6} Second, studies with different MCI definitions were included, although most studies used Petersen criteria⁴⁴ or criteria quite similar to Petersen criteria. Meta-regression findings showed that this did not affected our results. In addition, there was also heterogeneity in the depression scales, although meta-regression analysis indicated that this had no effect on the results. As stated earlier, heterogeneity in clinical studies was high and we could only partly explain this heterogeneity. Also, more information on the type, course and any received treatment of depression and depressive symptoms, e.g., history of depression and age of onset, would have given more insight into the kind of association, but was unfortunately not available in enough studies to perform meta-regression analysis. More information on the type, course and any received treatment

of the depressive symptoms could also have been useful to further understand the heterogeneity in the clinical studies.

In conclusion, we found strong evidence that depressive symptoms predict higher dementia risk in community-dwelling persons with MCI. More research is needed to identify the underlying mechanisms of this higher risk, particularly vascular risk factors should be taken into account and studies should differentiate between types of dementias. We found no significant association in clinical studies, but heterogeneity in these studies was very high.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Assessment of methodological quality*

	Criteria	Score
Sampling of patients	Consecutively referred or randomly selected	0 / 1
	Recruited as single cohort unclassified by disease state	0 / 1
	Tests performed at baseline	0 / 1
	Selection process fully described	0 / 0.5 / 1
	Referral process fully described	0 / 0.5 / 1
	Clinical and demographic characteristics fully described	0 / 0.5 / 1
	All eligible patients had undergone the tests or characteristics were compared	0 / 1
Reference diagnosis (dementia)	Methods and tests described in detail	0 / 0.5 / 1
	Positive and negative diagnosis clearly described	0 / 1
	Diagnosis likely to be close to truth	0 / 1
	Follow-up rate: at least 85%	0 / 1
	Same tests: diagnostic procedure at follow-up similar for all patients	0 / 0.5 / 1
	Blinding: researcher who made diagnosis of dementia at follow-up was blinded for baseline assessments	0 / 1
Assessment of depressive symptoms	Described how depressive symptoms were assessed	0 / 1
	Results clearly described	0 / 1
	Assessment performed in all eligible patients	
	All results described	0 / 1
Longitudinal design	Length of follow-up at least 3 years	0 / 1
	Low variability in follow-up length: 2 years or less	0 / 1

Scoring:

0 = missing (no information about the criterion) or absent (not fulfilling the criterion)

0.5 = incomplete information about the criterion or not completely fulfilling the criterion

1 = present

* Items derived from: Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ*. 2001;323(7306):224-228

Supplementary Table 2. Meta-regression analysis in clinical studies

Variable	Adjusted R-square	Coefficient	p
Mean age	1.62%	0.04	0.274
MDD as an exclusion criterion	-13.33%	0.12	0.627
Clinical diagnosis of depressive symptoms	11.74%	0.20	0.373
Use of GDS	-11.98%	0.02	0.927
Use of Petersen criteria	-0.59%	0.33	0.083
Mean MMSE score	47.64%	0.07	0.163
Mean follow-up duration	-7.34%	-0.04	0.634
Publication year	1.29%	-0.03	0.220
Conversion rate	-12.54%	0.00	0.930

MDD, major depressive disorder; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination

CHAPTER 3

DETERMINANTS OF QUALITY OF LIFE IN FAMILY CAREGIVERS IN MCI: A COMPARISON WITH MILD DEMENTIA

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ABSTRACT

Objectives

Being a family caregiver of a person with Mild Cognitive Impairment (MCI) can be challenging and may affect quality of life (QoL) of the caregiver. We aimed to investigate QoL of the family caregiver in MCI, explore possible determinants and study possible differences with being a family caregiver in mild dementia.

Methods

This secondary data analysis included 145 persons with MCI and 154 persons with mild dementia and their family caregivers from two Dutch cohort studies. Health-related QoL (HRQoL) was measured with the VAS of the EuroQoL 5D 3L version. Bivariate and multiple linear regressions analyses were conducted to examine a variety of potential determinants of the HRQoL of the caregiver.

Results

The mean EQ5D-VAS in family caregivers of persons with MCI was 81.1 (SD 15.7), and did not significantly differ from family caregivers in dementia (81.9 (SD 13.0)). In MCI, patient measurements such as the MMSE and the NPI were not significantly associated with caregiver mean EQ5D-VAS. Concerning caregiver characteristics, being a spouse and being older were associated with a lower mean EQ5D-VAS ($p=0.001$ and $p=0.033$ resp.). Also, caregivers with a higher educational level (low/middle vs. high: 78.6 (SD 17.8) vs. 84.2 (SD 12.1) $p = 0.032$) reported a higher EQ5D-VAS.

Discussion

Results indicate that especially family caregiver characteristics seem to influence family caregiver HRQoL in MCI. Future research should also examine other determinants such as burden, coping strategies, personality and relationship quality.

Keywords

Mild cognitive impairment; dementia; family caregiver; quality of life; EQ5D-VAS

INTRODUCTION

Mild cognitive impairment (MCI) is a common and important problem in older adults.¹ Despite the fact that by definition activities of daily living are largely intact in persons with MCI², supporting a family member with MCI can be challenging. In this article the term ‘family caregiver’ will also be used in MCI, although the caring is on a different level than in dementia³ and not all caregivers may actually identify themselves as providing care. The person with MCI may need assistance with (complex) tasks, behavioural problems may arise and the future may be uncertain. These changes may be significant stressors and lead to a reduced quality of life in the person with MCI and his or her caregiver. The World Health Organization defines quality of life as follows: ‘an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’.⁴ The WHO also explains that this is a complex concept and affected by multiple factors such as a person’s physical and psychological health and social relationships.⁴

In dementia extensive research has been done on caregiver quality of life⁵ and related caregiver outcomes such as caregiver burden.⁶ Limited research has been done on the quality of life of family caregivers supporting a person with MCI⁷, although previous research showed that approximately one third of caregivers of people with MCI report considerable levels of burden.⁸ Moreover, a study on outcome preferences for people with MCI and their caregiver showed that they both ranked quality of life of the patient and caregiver among the highest priorities, above for example patient functional status.⁹ Accordingly, multiple studies suggest that quality of life of the patient and the caregiver should more often be an important outcome in scientific research.^{7,10,11}

Determinants of quality of life in caregivers may not be straightforward, and not solely related to cognitive functioning of the person with cognitive impairment.¹² In dementia, studies examining quality of life in caregivers showed that neuropsychiatric symptoms are found to be associated with negative scores for quality of life of the family caregiver.¹³ Also, patient and family caregiver characteristics like gender, age and educational level may be of importance, although results are inconsistent.¹² In addition, it was found that the impact of psychosocial interventions in MCI on the caregiver QoL was especially associated with their own health and caregiver burden, and not that much with patient characteristics. However, the relatively small sample size might have influenced the results. A cross-sectional study on caregiver burden in MCI found that patient behavioural symptoms contributed most to caregiver burden.¹⁴ A qualitative study on quality of life of caregivers in MCI found that the caregiving influenced multiple aspects of the health-related quality of life (HRQoL).⁷ The most frequently discussed topic was social health, with a focus on role changes and inadequate support from others.

Systematic reviews show that interventions aiming to reduce burden and improve

quality of life of family caregivers are mainly focused on cognitive interventions on the person with MCI, sometimes together with psycho-education.^{15,16} The effects of these interventions seem limited. The idea behind these interventions is that improving the cognitive functioning of a person with MCI will lead to a better quality of life, also in the family caregiver. However, the question is whether cognitive functioning is the most important determinant of quality of life of the family caregiver of a person with MCI. In order to optimize interventions aiming to reduce burden and improve quality of life, more research on quality of life of family caregivers in MCI and related factors is needed. This leads to the following research questions:

1. What is the mean HRQoL of the family caregiver of a person with MCI, and is this different than in caring for a person with mild dementia?
2. What are determinants of HRQoL of the family caregiver of a person with MCI, and do these differ in the family caregiver of a person with mild dementia?

METHODS

Study design

A secondary data analysis was performed, using a selection of baseline data from two longitudinal studies: the Dutch Clinical Course of Cognition and Comorbidity in Mild Cognitive Impairment and Dementia (4C study)¹⁷ and from the LeARN study.¹⁸ The 4C study is a multicenter study and focuses on the course of cognitive decline in three Dutch memory clinics. The LeARN study is also a multicenter study of four Dutch memory clinics, and aimed at the diagnostic accuracy and cost-effectiveness of biomarkers while taking into account quality of life of the patient and the family caregiver.¹⁸ The present study included data from the following memory clinics who had relevant parameters of patients and caregivers available: Maastricht University Medical Centre, Maastricht; Radboud University Medical Center, Nijmegen; and Amsterdam UMC, Amsterdam.

Both studies were approved by the local medical ethics committees. Written informed consent was obtained for all participants. Detailed information about both studies can be found elsewhere.^{17,18}

Study population

The population of the original studies consisted of persons with subjective and/or objective memory complaints. Syndrome diagnoses of MCI and dementia at baseline were made based on clinical assessment by a multidisciplinary team. Persons were included if there was a reliable informant who visited or contacted the patient at least once a week. The most important exclusion criteria were the presence of other neurological disorders that could affect cognitive performance and if the participant was expected not to be available for follow-up. The inclusion and exclusion criteria were

comparable, the precise criteria are described in detail elsewhere.^{17,18} For this secondary analysis participants were selected if they were diagnosed with MCI or dementia and had data collected on family caregiver quality of life.

Patient measurements

In the original studies sociodemographic data such as age, gender, marital status and level of education were collected. All persons underwent a clinical assessment, which included a psychiatric, neurological and physical examination. History of the patient was taken including medication use and exploring comorbidities. For this secondary analysis, only psychiatric, cardiovascular and cerebrovascular co-morbidities were included in the analyses.

Neuropsychiatric symptoms were measured with the Neuropsychiatric Inventory (NPI).¹⁹ The NPI is a structured interview with an informant and consists of the assessment of the frequency and severity of 12 neuropsychiatric symptoms in the past 4 weeks (i.e., delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite/eating disturbances).¹⁹ Frequency (0 - 4) and severity (0 - 3) scores are multiplied to acquire a domain score per item, where higher scores indicate a more severe level of the neuropsychiatric symptom. For this study, presence of a neuropsychiatric symptom was included as a domain score (0-12) and furthermore domain scores were dichotomized (presence yes/no). Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE).^{20,21}

Activities of daily living were assessed by the Disability Assessment for Dementia (DAD).²² The ability to perform ten different basic and instrumental activities in daily functioning in the 2 weeks prior to the assessment was rated. The final DAD score is obtained by converting a sum score in a percentage from 0 to 100, a higher score indicates a higher level of daily functioning.

Primary outcome measure

HRQoL of the family caregiver was the primary outcome measure and was assessed with the Visual Analogue Scale (VAS) of the EuroQoL-5D (EQ-5D).²³ This scale ranges from 0 to 100 and is a way to record how a person scores his or her current HRQoL state (that day), with a higher score indicating a better HRQoL. The VAS was used to obtain the subjective rating of the HRQoL in accordance with previous studies.²⁴

Caregiver measurements

Sociodemographic data such as age, gender, marital status and level of education were collected. Also, the Care Related Quality of Life (CarerQoL) was used to assess the care-related quality of life.²⁵ The CarerQoL was not filled in by persons confirming the following remark: 'If you do not provide informal care, you can skip the other questions.'

The CarerQol consists of seven care-related burden items with a visual analogue scale (VAS) for happiness. The seven items are 1) fulfilment; 2) relational problems; 3) mental problems; 4) problems with daily activities; 5) financial problems; 6) support; and 7) physical problems.²⁵ The items are scored on a three-point scale (no, some and many) and result in a sum score. For this study the different items were binary coded (no/any) to avoid small cell count.

Informal care was assessed using the Resource Utilisation in Dementia - Lite instrument (RUD lite).²⁶ Caregivers were asked to report the amount of time spent on informal care concerning ADL (e.g., washing and grooming) and IADL (e.g., household activities, cooking), including supervision, during the last 30 days. Hours of informal caregiving were dichotomized into providing informal care or not.

Statistical analyses

Data was analyzed using SPSS version 23. Baseline differences between groups were analyzed using t-tests for continuous variables and chi-square tests for categorical variables. A complete case analysis was carried out, see supplementary figure 1 (flow chart).

Bivariate and multiple linear regression analyses were performed to explore possible associations between patient and caregiver characteristics and quality of life of the caregiver as measured by the EQ5D-VAS. First, patient and caregiver characteristics were included in bivariate analysis. In case the p-value was below 0.10 the variable was marked as potentially relevant and subsequently entered in the multivariable analysis.

In order to compare the determinants of the EQ5D-VAS, separate models were built for caregivers of persons with MCI and dementia. In addition, t-tests were performed in a subgroup of the sample who filled out the CarerQol questionnaire (i.e., those who identified themselves as caregivers) to explore differences in mean EQ5D-VAS across all seven CarerQol items.

RESULTS

Baseline characteristics

At baseline, 421 persons with cognitive problems and their family caregivers were included in the selection of centers of the original 2 studies. Of these, 299 persons and their caregivers had complete data, meaning data was available on all variables included for current analyses (supplementary figure 1; flow chart). Of these 299 persons, 145 were diagnosed with MCI and 154 were diagnosed with dementia. Comparison of the 122 persons and their caregivers with incomplete data versus the 299 persons and caregivers with complete data showed that persons with incomplete data were younger and the caregivers were more often spouses (see supplementary table 1). No significant

differences on MMSE scores were found.

Baseline characteristics of persons with MCI and dementia and their caregivers are presented in Tables 1 and 2 respectively. The mean EQ5D-VAS in caregivers of persons with MCI was 81.1 (SD 15.7), with a range of 20 to 100.

Results of bivariate analyses in MCI

Caregivers who cared for a female person with MCI had a mean EQ5D-VAS of 84.2 ± 12.9 and caregivers who cared for a male person with MCI had a mean EQ5D-VAS of 79.3 ± 17.0 ($p=0.068$). Other characteristics such as education, MMSE score, or NPI-total score of the person with MCI score were not associated with the caregiver EQ5D-VAS (see supplementary table 2). The DAD percentage showed a trend with bivariate linear regression (standardized Beta 0.151, $p=0.070$), a lower DAD percentage was associated with a lower EQ5D VAS. Concerning co-morbidity, only psychiatric co-morbidity of the person with MCI showed a trend towards an association with the caregiver EQ5D VAS (standardized Beta 0.139, $p=0.096$).

Table 1. Baseline characteristics of persons with MCI and dementia

Demographics	MCI n = 145	Dementia n = 154	P-value
Age, mean (SD)	72.1 (8.7)	76.1(9.0)	< 0.001
Females (%)	54 (37)	76 (49)	0.035
Education			0.033
Low (%)	59 (401)	75 (49)	
Middle (%)	30 (21)	41 (27)	
High (%)	56 (39)	38 (25)	
MMSE, mean (SD)	26.0 (2.6)	22.8 (3.3)	< 0.001
NPI total score, mean (SD)	13.7 (14.1)	20.3 (18.4)	0.001
Delusions, yes (%)	10 (7)	26 (17)	0.008
Hallucinations, yes (%)	6 (4)	10 (7)	0.366
Agitation/aggression, yes (%)	28 (19)	52 (34)	0.005
Depression, yes (%)	54 (37)	65 (42)	0.381
Anxiety, yes (%)	38 (26)	51 (33)	0.192
Euphoria, yes (%)	11 (8)	15 (10)	0.509
Apathy, yes (%)	66 (46)	86 (56)	0.074
Disinhibition, yes (%)	23 (16)	33 (21)	0.218
Irritability, yes (%)	61 (42)	69 (45)	0.633
Motor disturbances, yes (%)	12 (8)	29 (19)	0.008
Nighttime behavior, yes (%)	40 (28)	49 (32)	0.424
Eating problems, yes (%)	30 (21)	58 (38)	0.001
DAD percentage score, mean (SD)	82.9 (15.2)	68.9 (23.1)	< 0.001
Co-morbidity Psychiatry (%)	45 (31)	50 (33)	0.595
Co-morbidity Cerebrovascular (%)	31 (21)	28 (18)	0.308
Co-morbidity Cardiovascular (%)	87 (60)	94 (61)	0.604

Abbreviations: DAD, Disability Assessment for Dementia questionnaire; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; SD, standard deviation.

Table 2. Baseline characteristics of the family caregiver

Demographics	MCI	Dementia	p-value
Age, mean (SD)	62.3(12.0)	63.0 (11.7)	0.621
Females (%)	101 (70)	99 (64)	0.324
Education			0.727
Low (%)	26 (18)	33 (21)	
Middle (%)	54 (37)	53 (34)	
High (%)	65 (45)	68 (44)	
ADL care, yes (%)	21 (17)	63 (45)	<0.001
IADL care, yes (%)	48 (39)	101 (72)	<0.001
EQ5D-VAS	81.1 (15.7)	81.9 (13.0)	0.625

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living; EQ5D-VAS, Visual Analogue Scale of the EuroQoL-5D; MCI, mild cognitive impairment; SD, standard deviation.

Family caregivers who were younger (standardized Beta -0.177, $p=0.033$) and had a higher educational level (low/middle vs. high: 78.6 (SD 17.8) vs. 84.2 (SD 12.1) $p = 0.032$) reported higher EQ5D-VAS. Gender of the family caregiver was not associated with the EQ5D-VAS. Regarding the relationship of the caregivers, children and 'others' reported a higher EQ5D-VAS than spouses (standardized Beta -0.272, $p=0.001$). Also, in family caregivers providing care with IADL lower EQ5D-VAS were reported (standardized Beta -1.07, $p = 0.084$), see supplementary table 2).

Results from multivariable linear regression analysis in MCI

Characteristics with a p -value below 0.1 in the bivariate analysis were included. Collinearity statistics showed acceptable values (max VIF < 2.0), except for the variables age of the caregiver and relationship between the caregiver and the person with cognitive symptoms, with spouses being older than other caregivers (mainly daughters / sons). Therefore, these variables were not entered in the analyses together.

In the multivariable model with relationship, relationship was a significant predictor of the EQ5D-VAS of the caregiver ($B=8.075$, $p = 0.013$, R square of the model 0.153). The other predictors did not show a significant association anymore. In the multivariable model with age of the caregiver, education of the caregiver was a significant predictor of the EQ5D-VAS of the caregiver ($B 6.162$, $p = 0.037$, R square of the model 0.125), other predictors were not significant.

A comparison with dementia

The mean EQ5D-VAS of caregivers of persons with dementia was 81.9 (SD 13.0), with a range of 40 to 100. The EQ5D-VAS of caregivers was not significantly different in MCI and mild dementia.

In dementia, patient characteristics such as age, education and MMSE score were not associated with caregiver EQ5D-VAS, which was comparable to the MCI-group. Unlike in MCI, total NPI score and different NPI items, namely apathy, disinhibition,

irritability, nighttime behavior and eating problems showed an association or a trend (see supplementary table 3).

In dementia, a multiple linear regression analysis was run with the NPI items with a p-value below 0.10 in the bivariate analyses. None of the separate NPI items were significant.

Subgroup analysis with the CarerQol

A subgroup of the caregivers completed the CarerQol, namely, the caregivers who identified themselves as persons providing actual care to the person with MCI or dementia. In MCI, caregivers reporting problems with their own mental and/or physical health and caregivers reporting problems combining care tasks with daily activities had a lower mean EQ5D VAS (see Table 3). In dementia this was the same, but also caregivers reporting relational problems with the care receiver had a significantly lower mean EQ5D VAS.

Table 3. CarerQol and mean EQ5D VAS in MCI and dementia

CarerQol item	MCI			Dementia		
	No	Yes	p-value	No	Yes	p-value
Fulfillment from carrying out my care tasks	75.2 ± 16.4 N = 12	79.7 ± 17.3 N = 81	0.397	79.4 ± 15.1 N = 9	81.9 ± 13.1 N = 120	0.591
Relational problems with the care receiver	82.3 ± 18.6 N = 56	76.1 ± 13.9 N = 41	0.077	85.1 ± 11.9 N = 58	78.4 ± 14.0 N = 73	0.005
Problems with my own mental health	85.2 ± 16.4 N = 49	73.6 ± 15.9 N = 48	0.001	86.0 ± 10.8 N = 65	76.8 ± 14.3 N = 67	<0.001
Problems combining care tasks with my daily activities	83.2 ± 14.5 N = 61	72.4 ± 19.1 N = 35	0.005	85.0 ± 10.6 N = 58	78.4 ± 15.1 N = 70	0.004
Financial problems because of my care tasks	79.9 ± 16.0 N = 92	71.0 ± 19.5 N = 5	-	81.9 ± 13.4 N = 120	74.5 ± 13.7 N = 11	0.082
Support with carrying out my care tasks, when I need it	82.7 ± 14.7 N = 27	78.1 ± 17.8 N = 68	0.231	78.6 ± 15.9 N = 33	82.2 ± 12.2 N = 96	0.182
Problems with my own physical health	86.8 ± 12.7 N = 52	71.0 ± 17.9 N = 44	<0.001	87.4 ± 10.1 N = 76	73.1 ± 13.2 N = 56	<0.001

Data are presented as mean EQ5D-VAS ± SD

DISCUSSION

To our knowledge this is one of the first studies focusing on the Health-Related Quality of Life (HRQoL) of family caregivers in MCI, as measured with the EQ-5D VAS. Results indicated that the HRQoL of family caregivers in MCI did not differ from that in mild dementia, and furthermore showed that mainly caregiver characteristics were associated with their HRQoL.

We did not find a difference in HRQoL in family caregivers in MCI versus mild dementia, neither did we find an association with global cognition. These findings are in

line with previous studies in caregivers with dementia finding no or minimal association with cognition.^{27–29} A previous, cross-sectional, study on distress in MCI caregivers also found evidence that cognitive measures were not associated with caregiver distress.³⁰ A possible explanation is that the way the caregiver is able to cope with the situation is more important than the objective impairments, including cognition.⁵ This can be explained with the concept of the ‘disability paradox’: a fair amount of people with disabilities is able to adapt and maintain a good quality of life.³¹ It is thought that these people are able to find and maintain a balance between physical and mental health, and their social context.³¹ The same might be true for family caregivers in MCI, some may be able to adapt quickly to the start of their ‘caregiver career’.³² Also, the HRQoL of the family caregivers was relatively high compared to Dutch population norms in the same age group.³⁵ This is a hopeful finding: caring for someone with MCI or mild dementia might have little impact on the caregiver’s HRQoL.

In MCI, no association was found between family caregivers’ HRQoL and neuropsychiatric symptoms of the person with MCI. A possible explanation for not finding an association in MCI might be that the prevalence and severity of neuropsychiatric symptoms in MCI were relatively mild (mean NPI-total score of 13.7 (SD 14.1) in MCI; mean score 20.3 (SD 18.4) in dementia), which is in line with other studies.^{33,34} In dementia, some neuropsychiatric symptoms (i.e., apathy, disinhibition, irritability, nighttime behavior and eating problems) were significantly associated with caregivers’ QoL in our study. However, although neuropsychiatric symptoms are thought to influence caregivers’ QoL in dementia³⁶, evidence is not consistent.⁵

Another explanation for not finding an influence of cognition or neuropsychiatric symptoms is the fact that the EQ5D-VAS is a generic measure of the health-related QoL. Although the EQ5D, including the related VAS, is a way to measure subjective well-being and QoL in cognitive disorders^{24,37}, it is not a burden scale and not designed to measure the impact of caring for a person with cognitive problems.³⁸

In the present study, being a spouse was associated with a lower HRQoL, which is in line with previous research.⁵ It should be noted that spouses are generally older, and age has been found to be associated with a lower HRQoL.³⁵

A subgroup of the caregivers in our study completed the 7 items of the CarerQoL, these data were used to explore a possible impact on the HRQoL of the caregivers. We interpreted these results with caution because of selection bias (only family caregivers who identified themselves as carers filled in the CarerQoL) and because the CarerQoL, partly, measures the same outcome as the EQ5D-VAS. Caregivers reporting problems with their own mental and/or physical health and caregivers reporting problems combining their care tasks with their daily activities had lower EQ5D-VAS scores. This is in line with earlier studies that found that caregiver’s physical and mental health was most consistently associated with QoL.^{5,12} One of these studies found that mental health related problems of caregivers themselves (depression and burn-out) were more

associated with caregiver quality of life than patient-related variables.²⁷

In dementia, but not in MCI, caregivers reporting relational problems and caregivers reporting a lack of support on the CarerQol scored a significantly lower EQ5D-VAS. An earlier study in dementia suggests that dyadic coping and relationship quality are very important for the caregiver and functions as a mediator between stress and quality of life in caregivers.³⁹ It could be that support and dyadic coping get more important when the situation becomes more complex, and therefore be more important in dementia than in MCI.

This study has several strengths. First, it consists of two well-designed multicenter studies of memory clinic visitors. Furthermore, many patient and family caregiver factors were taken into account, and because of that, multiple possible determinants could be tested in the regression models. However, as this was a secondary data analysis, specific characteristics such as coping strategies of caregivers were not available and could not be included. Factors such as negative emotions, optimism and caregiver profiles showed to be associated with QoL in previous dementia research.^{40–42} One other limitation relates to the sample size. The sample was divided between syndrome diagnosis (MCI and dementia) and furthermore a selection was made based on availability of data, resulting in a smaller sample. Last, the present population consists of memory clinic visitors, therefore, results should not be generalized to the general population.

CONCLUSION

This explorative study was one of the first examining HRQoL in family caregivers of people with MCI. Results suggest that in MCI mainly caregiver characteristics explain family caregiver QoL as measured with the EQ5D-VAS. Neither neuropsychiatric symptoms nor cognition of the person with MCI were associated with the HRQoL. Being a spouse and being older was associated with a lower QoL. The present study is a starting point, and future work is needed to further analyze determinants of family caregiver QoL in MCI taken into account determinants such as burden, coping strategies, personality and relationship quality.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Comparison of persons with incomplete vs. complete data on demographics.

Demographics	Data incomplete (n=122)	Data complete (n=299)	P-value
<u>Patient</u>			
Age (SD)	68.6 (9.7)	74.1 (9.0)	< 0.001
Gender, female (%)	52 (43)	130 (44)	0.480
MMSE (SD)	24.8 (3.3)	24.4 (3.4)	0.220
<u>Family caregiver</u>			
Age (SD)	61.8 (11.3) ¹	62.6 (11.9)	0.598
Gender, female (%)	45 (63) ²	200 (67)	0.491
Relationship, spouses (%)	57 (80)	179 (60)	0.001

Abbreviations: MMSE, Mini-Mental State Examination; SD, standard deviation

¹ Data available in 61 of 122 family caregivers

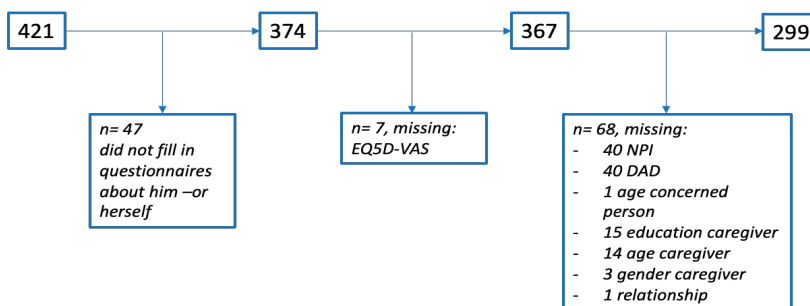
² Data available in 71 of 122 family caregivers

Supplementary Table 2. Bivariate analysis of factors affecting the EQ5D VAS among family caregivers of persons with MCI

Variables	Unstandardized B	Standardized Beta	P-value
<u>Persons with MCI</u>			
Age	0.028	0.016	0.851
Gender	4.929	0.152	0.068
Education: Low vs. Middle/high	0.214	0.007	0.936
MMSE	0.751	0.125	0.134
NPI total score	-0.041	-0.036	0.664
Delusions, y/n	2.567	0.042	0.620
Hallucinations, y/n	3.014	0.038	0.647
Agitation, y/n	3.445	0.087	0.301
Depression, y/n	1.123	0.035	0.679
Anxiety, y/n	-4.429	-0.124	0.136
Euphoria, y/n	-1.595	-0.027	0.747
Apathy, y/n	-3.011	-0.096	0.252
Disinhibition, y/n	-1.320	-0.031	0.713
Irritability, y/n	-1.662	-0.052	0.531
Motor disturbance	-2.937	-0.052	0.537
Nighttime behavior	2.161	0.062	0.461
Eating problems	1.164	0.030	0.719
DAD percentage	0.156	0.151	0.070
<u>Co-morbidity</u>			
Cardiovascular	0.851	0.027	0.751
Cerebrovascular	-1.409	-0.010	0.900
Endocrine	1.077	0.030	0.718
Psychiatric	4.703	0.139	0.096
<u>Caregivers</u>			
Age (SD)	-0.232	-0.177	0.033
Gender	-4.149	-0.122	0.144
Education, low/middle vs. high	5.600	0.178	0.032
Relationship, spouse vs. other	-9.053	-0.272	0.001
Caregiving in ADL, y/n	-0.914	-0.30	0.608
Caregiving in IADL y/n	-3.122	-1.07	0.084

Supplementary Table 3. Univariate analysis of factors affecting the EQ5D VAS among family caregivers of persons with dementia

Variables	Unstandardized B	Standardized Beta	P-value
<u>Persons with dementia</u>			
Age	-0.012	-0.008	0.928
Gender	3.135	0.121	0.136
Education: Low vs. Middle/high	-0.413	-0.016	0.845
MMSE	-0.382	-0.097	0.230
NPI total score	-0.107	-0.150	0.065
Delusions, y/n	-0.003	0.000	0.999
Hallucinations, y/n	1.791	0.034	0.675
Agitation, y/n	-2.210	-0.081	0.321
Depression, y/n	-0.230	-0.009	0.914
Anxiety, y/n	-1.090	-0.040	0.626
Euphoria, y/n	-0.674	0.015	0.850
Apathy, y/n	-4.018	-0.154	0.057
Disinhibition, y/n	-4.842	-0.153	0.058
Irritability, y/n	-4.250	-0.163	0.044
Motor disturbance	-3.944	-0.119	0.142
Nighttime behavior	-3.886	-0.139	0.084
Eating problems	-3.614	-0.135	0.095
DAD percentage	0.054	0.096	0.234
<u>Co-morbidity</u>			
Cardiovascular	0.291	0.013	0.869
Cerebrovascular	-1.382	-0.058	0.474
Endocrine	1.908	0.085	0.297
Psychiatric	2.148	0.099	0.221
<u>Caregivers</u>			
Age (SD)	-0.140	-0.126	0.120
Gender	-2.266	-0.084	0.302
Education, low/middle vs. high	0.397	0.015	0.852
Relationship, spouse vs. other	-3.205	-0.123	0.128
Time spent in caregiving ADL, hours per day	-0.953	-0.198	0.019
Time spent in caregiving IADL, hours per day	-0.789	-0.130	0.127
Caregiving in ADL, y/n	-0.972	-0.039	0.647
Caregiving in IADL y/n	-1.827	-0.065	0.442



Supplementary Figure 1. Flow chart to complete case analysis

CHAPTER 4

TRAJECTORIES OF RELATIONSHIP QUALITY IN DEMENTIA: A LONGITUDINAL STUDY IN EIGHT EUROPEAN COUNTRIES

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ABSTRACT

Objectives

Relationship quality (RQ) between a person with dementia and a family carer may influence their health and quality of life. However, evidence regarding its course and influencing factors is limited. We aimed to explore RQ trajectories in dementia, and identify predictors of change.

Methods

We analysed longitudinal data from a cohort of 350 community-dwelling people with dementia and their informal carers, participating in the Actifcare study in eight European countries. The Positive Affect Index, rated separately by both people with dementia and their carers, assessed RQ. Other measures included the Neuropsychiatric Inventory Questionnaire (regarding persons with dementia), and the Relative Stress Scale, Sense of Coherence Scale and Lubben Social Network Scale (for carers). Trajectories and influencing factors were explored applying a latent growth model (LGM).

Results

RQ in the group of carers declined over 1 year, but RQ scores for the persons with dementia did not change. Higher stress in carers negatively influenced their baseline RQ ratings. Carer sense of coherence and being a spouse were associated with more positive baseline RQ carer assessments. Higher levels of neuropsychiatric symptoms were linked to decline in carers' RQ, whereas social support was associated with more positive RQ trajectories.

Conclusion

This study provides a valuable insight into the course of RQ. LGM proved useful to explore the factors that influence RQ trajectories and variability within- and between-persons. Our findings emphasise the importance of carer-perceived social support and sense of coherence, and of reducing neuropsychiatric symptoms, in maintaining a good RQ.

INTRODUCTION

Relationship quality (RQ) between persons with dementia and their supporters, mostly family carers, may influence quality of life (QoL) in both.¹⁻⁶

Some studies also suggest worse RQ is associated with outcomes such as challenging behaviours, cognitive and functional decline or institutionalization.^{7,8} Research indicates that RQ is a dynamic process and may change, especially from the perspective of carers, as dementia severity increases.⁹⁻¹¹ It is therefore important to determine which factors protect RQ over time.

A review of qualitative studies found that persons with dementia and their family carers try to maintain a sense of ‘togetherness’¹², despite the challenges and uncertainties accompanying dementia. However, the presence of difficulties such as behavioural problems may have a negative impact on RQ.⁴

Person with dementia and carer perspectives on RQ are particularly affected by factors such as carer stress¹³, depression and anxiety¹⁴, social isolation¹⁵ and neuropsychiatric symptoms of the person with dementia⁷. Our previous cross-sectional study of baseline data from a large European cohort study of people with dementia and their primary carers supported these findings.¹³ It also highlighted sense of coherence (SOC) and spouse/partner relationship type as potential protective factors of RQ meriting further evaluation. There is clearly scope for identifying other RQ predictors: in our study¹³, as in other studies¹⁰ a fair amount of variance in predictive models remained unexplained.

Evidence from longitudinal studies analysing the course and determinants of RQ is sparse. In young-onset dementia, RQ, as perceived by spouses, deteriorated over time.⁹ Multiple factors were associated with lower RQ, including symptom duration, hyperactivity, apathy and less initiative toward performing daily living activities. Other longitudinal studies also found that carer RQ ratings declined¹⁰ and that RQ is influenced by stress, depression and anxiety in the carer, and neuropsychiatric symptoms and self-reported QoL of the person with dementia.^{10,11}

However, the few available longitudinal studies relied on relatively small convenience samples^{10,11}, short follow-up periods (6 months)¹¹ or participants with particular profiles, such as higher anxiety in dementia¹¹ and young-onset dementia, or focused mainly on RQ outcomes and not determinants.^{8,16-18}

Moreover, these studies used variable-centred methodologies such as multiple regression, factor analysis and analysis of variance.^{8,10,11,17,18} To the best of our knowledge, the application of a statistical method such as latent growth model (LGM) to the understanding of RQ in dementia is novel. LGMs consist of variable based analyses that takes into account both within-person changes and between-person differences in individuals’ change trajectories.¹⁹⁻²² Therefore, the present study aims to employ LGM to understand the course of RQ and its determinants in a large cohort of dementia caregiving dyads, examining a broader range of influences than considered in previous

studies. These include RQ risk factors potentially amenable to intervention. Specifically, the influence of SOC, type of relationship and psychological and social unmet needs are evaluated alongside other recognised potentially modifiable risk factors, including neuropsychiatric symptoms, and carer stress, depression and anxiety.

The linkage between RQ perspectives of carers and people with dementia (interdependence) also merits further research. Some studies have explored the reciprocal influence of RQ, regarding specific outcomes. For example, higher perceived RQ among carers was positively associated with better ratings of QoL by people with dementia.¹ Findings from a cross-sectional analysis⁵ revealed that for each member of the dyad, their perceptions of RQ were significantly related to their own life satisfaction and well-being (an ‘actor effect’²³) but had no significant impact on the wellbeing and life satisfaction of the other member of the dyad (a ‘partner effect’²³). To our knowledge, no study has explored yet how the RQ perspectives of each member of the dyad impact on the perceived RQ of the other, although this information could inform timely psychosocial interventions, with a relationship focus.

Accordingly, we aimed firstly to examine changes in RQ longitudinally over a 12-month period in persons with dementia and carers, and to describe individual differences in these trajectories over time. Secondly, we aimed to consider the influence of a broad range of variables on RQ levels and trajectories.

MATERIALS AND METHODS

We studied a community-dwelling sample of people with mild-to-moderate dementia and their informal (family) carers participating in the Actifcare (ACcess to TImely Formal Care) EU-JPND project. Actifcare was a 1-year prospective cohort and multimethod study focusing on dementia formal care in the community in eight European countries: Germany, Ireland, Italy, Netherlands, Norway, Portugal, Sweden and United Kingdom. Our previous study on RQ analysed baseline data from this cohort.¹³

In the present study we used longitudinal data (three assessments: baseline, 6 and 12-month follow-ups), collected between November 2014 and August 2016, from people with dementia and their family carers (451 dyads). The Actifcare cohort study protocol is detailed elsewhere.²⁴

Participants

Participants were people with mild-to-moderate dementia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)²⁵ and the Clinical Dementia Rating (CDR)²⁶, and their informal carers (being in contact at least once a week). Clinicians in charge assessed the participants’ severity of dementia, also confirmed by researchers.²⁴ Exclusion criteria included alcohol-related dementia or Huntington’s disease, and receipt

of significant (personal) care from formal services at baseline because of dementia. Participants were recruited from various settings, including general practices, memory clinics and Alzheimer's Associations.²⁴ Demographic and clinical characteristics of the Actifcare cohort at baseline are also detailed elsewhere (n = 451 dyads).^{13,24}

Measures

Comprehensive assessments were conducted by trained staff²⁴, mostly at the participants' homes. Only the main measures used here are outlined below. Baseline variables possibly influencing carer and person with dementia RQ ratings were chosen based on the literature, including our previous findings.¹³ When validated national versions were not available, instruments were translated and careful translation-back translation procedures helped to ensure validity and reliability. The Positive Affect Index (PAI)²⁷ assessed current perceived RQ, and was rated separately by both persons with dementia and their carers. This 5-item scale comprises five questions addressing closeness, communication, similar views, shared activities and generally getting along. An example of an item is 'how is communication between yourself and your relative/friend, how well can you exchange ideas or talk about things that really concern you?'. Responses are rated on a 6-point scale from 1 (not well) to 6 (extremely well), with a total sum score ranging from 5 to 30 (higher scores reflecting better RQ). This scale has been used with people with dementia^{4,10}, showing good internal consistency (Cronbach α .81) and reasonable test-retest reliability over 12 weeks ($r = .66$).²⁸ In the present study, Cronbach's α 's were 0.82 (people with dementia) and 0.79 (carers).

Person with dementia measures

Measures for people with dementia included: CDR²⁶, Mini Mental State Examination (MMSE)²⁹, a version of the Neuropsychiatric Inventory Questionnaire (NPI-Q), with symptom count and separate scores for severity and carer distress³⁰, Instrumental Activities of Daily Living (IADL) and Physical Self-Maintenance Scale (PSMS)³¹. The NPI-Q, IADL and PSMS were completed from the carer's report. The Camberwell Assessment of Need (CANe) was used to assess 24 areas of individual needs (environmental, health, social and psychological) and to record separately the perspectives of the people with dementia, carer and researcher.³² For each specific area (e.g. Does the person have difficulty in looking after their home?), responses are rated on a three point scale: 0 – no need, 1 – met need (problem receiving appropriate intervention or assessment) and 2 – unmet need (problem not receiving appropriate assessment or intervention). We considered the researcher's perspective (based on both person and carer's perspectives and all other information gathered through the assessment) regarding the total number of needs judged to be unmet.

Carer measures

Carers completed the Hospital Anxiety and Depression Scale (HADS)³³ and the Relative Stress Scale (RSS).³⁴ Carer's perceived social network was measured with the Lubben Social Network Scale (LSNS-6).³⁵ The 13-item version of the SOC scale was used to assess carer's sense of coherence.^{36,37} Two CANE items evaluate carers' needs: information and psychological distress.³²

Ethical considerations

The study protocol was approved by ethics committees in each of the eight countries. The carer and the person with dementia both gave written informed consent according to national regulations.

Statistical analysis

For this longitudinal analysis, only dyads providing sufficient data on the PAI scale at all three time points were considered (350 dyads). Conditional Latent Growth Models (LGM) for both persons with dementia and carers were fitted to the data with the lavaan package³⁸ from the R Statistical Software System.³⁹

Missing data for variables with less than 10% missing were imputed using the Full Information Maximum Likelihood (FIML) method present in the lavaan package. No severe deviations to normality were observed in PAI scores ($|Sk| < 3$ and $|ku| < 7$) and thus Maximum Likelihood methods were appropriate for LGM.⁴⁰

LGM assumes that the observed variations can be explained by two latent factors – the intercept (in this analysis, the initial level of RQ) and the slope (change rate of RQ) – that quantify the variation both at group level (fixed effects, the mean of the latent factor) and at individual level (random effects, the variance of the latent factor that estimates interindividual heterogeneity around the mean and the intraindividual variability over time.⁴¹ The analysis of individual effects versus group effects is conducted with significance tests on the means and variances of the intercept and slope.

Models were fitted using maximum likelihood and goodness of fit was assessed with the statistic, Goodness of Fit Index (GFI), Tucker Lewis Index (TLI) and Standardized Root Mean Square Residual (SRMR). Since LGM have generally reduced degrees of freedom, the use of Root Mean Square Error of Approximation (RMSEA) is not recommended.⁴⁰ Non-significant, GFI and TLI larger than 0.95 and SRMR smaller than 0.05 were considered indicative of good model fit.⁴²

RESULTS

Table 1 provides details of the demographics of the included sample (n = 350 dyads) and their scores on measures at baseline. Table 2 provides descriptive statistics for the PAI at the three time points.

Table 1. Characteristics and summary of measures of people with dementia and their carers at baseline

Person with dementia (n= 350)	
Sex, women, n (%)	169 (52.6)
Age, years, mean (SD, range)	76.8 (7.8, range 47-94)
Education, years, mean (SD)	10.1 (4.5)
Living alone, n (%)	81 (25.2)
Type of dementia, n (%)	
Alzheimer's disease	176 (50.3)
Vascular	35 (10.0)
Mixed vascular/Alzheimer's disease	42 (12.0)
Lewy Body	4 (1.1)
Other	24 (6.9)
Unspecified/unknown type of dementia	69 (19.7)
Cognitive impairment (MMSE), mean (SD)	19.2 (5.0)
Dementia severity (CDR), n (%)	
1 (Mild)	342 (97.7)
2 (Moderate)	8 (2.3)
Neuropsychiatric symptoms (NPI-Q), mean (SD)	7.3 (5.4)
Severity (NPI-Q), mean (SD)	7.8 (5.1)
IADL function (IADL), mean (SD)	3.5 (1.9)
Basic ADL function (PSMS), mean (SD)	3.9 (1.8)
Unmet needs (CANE), mean (SD), range	1.6 (1.8, 0-10)
Carer (n= 350)	
Sex, female, n (%)	209 (65.1)
Age, years, mean (SD, range)	66.7 (13.2, range 28-92)
Education, years, mean (SD)	12.0 (4.5)
Relationship to the person with dementia, n (%)	
Spouse/partner	235 (67.1)
Adult children	96 (27.4)
Other (e.g. son/daughter in law; sibling)	19 (5.4)
Depression (HADS), mean (SD)	4.3 (3.5)
Anxiety (HADS), mean (SD)	5.9 (3.9)
Distress (NPI-Q), mean (SD)	8.7 (7.0)
Perceived social support (LSNS-6)	16.6 (5.6)
Stress (RSS), mean (SD)	20.31 (10.5)
Sense of coherence (SOC), mean (SD)	67.6 (10.9)
Psychological distress unmet needs (CANE), mean (SD, range)	1.0 (2.1, 0-9)
Information unmet needs (CANE), mean (SD, range)	1.1 (1.0, 0-9)

Abbreviations: CDR, Clinical Dementia Rating Scale; HADS, Hospital Anxiety and Depression Scale; IADL, Instrumental Activities of Daily Living; MMSE, Mini Mental State Examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; PSMS, Physical Self-Maintenance Scale; LSNS-6, Lubben Social Network Scale; RSS, Relatives' Stress Scale; SOC, Sense of Coherence.

Table 2. Descriptive statistics for Relationship Quality (PAI)

Variable	n participants	n missing participants	Completeness rate of PAI scale	M	SD	Sk	Ku	Histogram
PwD RQ (T0)	350	5	0.99	22.85	3.94	-0.78	1.28	
PwD RQ (T1)	350	29	0.92	22.40	3.86	-0.83	1.20	
PwD RQ (T2)	350	52	0.85	22.60	3.74	-0.58	0.73	
Carer RQ (T0)	350	6	0.98	21.31	4.42	-0.36	-0.14	
Carer RQ(T1)	350	15	0.96	20.71	4.31	-0.26	-0.29	
Carer RQ (T2)	350	9	0.97	19.82	4.55	-0.11	-0.34	

Abbreviations: PwD, Person with dementia; PAI, Positive Affect Index; M, Mean; RQ, Relationship Quality; SD, Standard Deviation; Sk, Skewness; Ku, Kurtosis

Relationship quality trajectories among persons with dementia and carers

The overall LGM for persons with dementia (Figure 1) had a good fit to the longitudinal data at the three time points $\chi^2(1) = 3.74$, CFI = 0.99, NFI = 0.99, TLI = 0.97, SRMR = 0.02). The mean RQ at baseline was $\beta_0 = 22.745$; $p < .001$ and the mean RQ growth rate $\beta_1 = -0.159$; $p = 0.116$. Although the RQ growth trajectory for the entire group of persons with dementia did not change significantly over the 12-month period, there was a degree of individual variation within the group in their baseline RQ levels ($\text{Var}(\beta_0) = 10.902$, $p < .001$). However, no significant variation in individual RQ growth trajectories over time was observed ($\text{Var}(\beta_1) = 0.993$; $p = 0.123$) (see appendix A1 published as supplementary material online).

Regarding carers, the overall LGM (Figure 1) had a good fit to the longitudinal data at T0, T1 and T2 ($\chi^2(1) = 1.07$, CFI = 1, NFI = 1, TLI = 1, SRMR = 0.01). The mean RQ baseline level was $\beta_0 = 21.370$; $p < .001$ and the mean RQ growth rate $\beta_1 = -0.762$; $p < .001$. Carer RQ ratings declined significantly over time. There were significant interindividual differences among the carers in their baseline RQ levels ($\text{Var}(\beta_0) = 13.099$, $p < .001$) but no individual variation in the growth curve within the group was observed ($\text{Var}(\beta_1) = 0.191$; $p = 0.780$) (see appendix A2 published as supplementary material online).

Baseline determinants of relationship quality trajectories

We examined a number of potential baseline influences on RQ trajectories of persons with dementia and carers. For persons with dementia, we considered person with dementia unmet needs and carers' RQ perspective, stress, perceived social support, psychological distress unmet needs, and type of care relationship (i.e. spouse or adult child). Only RQ as rated by the carer showed a significant positive association with the baseline (intercept) perceived RQ of the person with dementia $\beta = 0.431$; $p < .001$ (Table 3). No statistically significant effects were observed for RQ change over time (slope, β_1) regressed on the conditioning variables.

Regarding the baseline factors influencing carers' rated RQ, increased levels of carer stress ($\beta = -0.262$, $p = .002$) related to lower baseline RQ (intercept) among carers (Table 4). RQ, as rated by the person with dementia ($\beta = 0.357$, $p < .001$), carer SOC ($\beta =$

0.190, $p = .005$) and being a spouse (compared to adult child carer) ($\beta = 0.198$, $p = .001$) were positively correlated with the baseline RQ level of carers. Higher levels of baseline neuropsychiatric symptoms ($\beta = -.839$, $p = .034$) influenced the decline of the carers' RQ growth curve over 1 year. Carer perceived social support ($\beta = 0.673$, $p < .045$) and person with dementia unmet needs ($\beta = 0.916$, $p < .010$) positively influenced RQ over time.

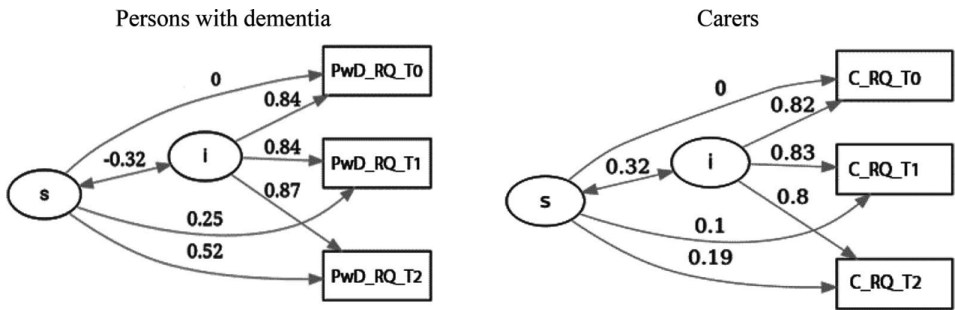


Figure 1. Path diagram for persons with dementia and carers' latent growth curve model. Abbreviations: C, Carer; i, Intercept; PwD, Person with dementia; RQ, Relationship Quality; s, Slope; T0, baseline; T1, follow-up at 6 months; T2, follow-up at 12 months. By convention, circles (or ellipses) represent unobserved/latent variables (intercept and slope), squares (or rectangles) represent observed/measured variables (here RQ at T0, T1 and T2 are equally spaced repeated measures). The double-headed arrow represents the covariance between the latent intercept and slope, and single-headed arrows represent regression weights. The intercept is the initial level of RQ, measured by PAI scale, and the slope represents the rate in change of RQ over time. Each participant has an estimated intercept and slope, and these are allowed to vary across individuals. Latent variables also have means, reflecting the average of all participants' intercepts and slopes.

Table 3. Summary of LGM analysis for the baseline variables predicting Relationship Quality (PAI) trajectories among persons with dementia (factor loadings).

Latent Factor	Indicator	Beta	SE	Z	Sig
i	Carer Relationship Quality (PAI)	0.431	0.050	6.546	0.000
i	Relative Stress Scale (RSS)	0.084	0.022	1.185	0.236
i	Perceived social support of carer (LSNS-6)	0.027	0.036	0.451	0.652
i	PwD unmet needs (CANE)	-0.120	0.115	-1.950	0.051
i	Carer psychological distress unmet needs (CANE)	-0.001	0.537	-0.023	0.982
i	Spouse/partner relationship to the PwD	0.062	0.426	1.031	0.303
s	Carer Relationship Quality (PAI)	0.052	0.026	0.444	0.657
s	Relative Stress Scale (RSS)	0.164	0.012	1.306	0.191
s	Perceived social support of carer (LSNS-6)	0.023	0.019	0.221	0.825
s	PwD unmet needs (CANE)	0.111	0.061	1.007	0.314
s	Carer psychological distress unmet needs (CANE)	-0.038	0.282	-0.325	0.745
s	Spouse/partner relationship to the PwD	-0.037	0.218	-0.351	0.726

Abbreviations: CANE, Camberwell Assessment of Need for the Elderly; i, Intercept; LSNS-6, Lubben Social Network Scale; PAI, Positive Affect Index; PwD, Person with Dementia; RSS, Relatives' Stress Scale; s, Slope.

Table 4. Summary of LG M analysis for the baseline variables predicting Relationship Quality (PAI) trajectories among carers (factor loadings).

Latent Factor	Indicator	Beta	SE	Z	Sig
i	Basic ADL function (PSMS)	-0.023	0.117	-0.390	0.696
i	Neuropsychiatric symptoms (NPI-Q)	-0.062	0.042	-0.987	0.323
i	PwD Relationship Quality (PAI)	0.357	0.049	6.577	0.000
i	Sense of Coherence (SOC)	0.190	0.022	2.807	0.005
i	Anxiety (HADS)	0.022	0.071	0.288	0.773
i	Depression (HADS)	-0.127	0.082	-1.578	0.115
i	Relative Stress Scale (RSS)	-0.272	0.029	-3.173	0.002
i	Perceived social support of carer (LSNS-6)	0.066	0.036	1.202	0.229
i	PwD unmet needs (CANE)	-0.072	0.116	-1.268	0.205
i	Carer psychological distress unmet needs (CANE)	0.044	0.527	0.722	0.470
i	Spouse/partner relationship to the PwD	0.198	0.427	3.509	0.000
s	Basic ADL function (PSMS)	0.245	0.057	0.675	0.500
s	Neuropsychiatric symptoms (NPI-Q)	-0.839	0.021	-2.122	0.034
s	PwD Relationship Quality (PAI)	-0.486	0.024	-1.423	0.155
s	Sense of Coherence (SOC)	0.263	0.011	0.619	0.536
s	Anxiety (HADS)	0.421	0.035	0.877	0.381
s	Depression (HADS)	0.634	0.040	1.257	0.209
s	Relative Stress Scale (RSS)	-0.395	0.014	-0.731	0.465
s	Perceived social support of carer (LSNS-6)	0.673	0.018	1.921	0.045
s	PwD unmet needs (CANE)	0.916	0.056	2.561	0.010
s	Carer psychological distress unmet needs (CANE)	0.464	0.258	1.221	0.222
s	Spouse/partner relationship to the PwD	-0.205	0.209	-0.577	0.564

Abbreviations: CANE, Camberwell Assessment of Need for the Elderly; HADS, Hospital Anxiety and Depression Scale; i, Intercept; LSNS-6, Lubben Social Network Scale; NPI-Q, Neuropsychiatric Inventory Questionnaire; PAI, Positive Affect Index; PSMS, Physical Self-Maintenance Scale; RSS, Relatives' Stress Scale; s, Slope; SOC, Sense of Coherence.

DISCUSSION

In this one-year longitudinal study, we examined trajectories of RQ and its influencing factors in a large European sample of persons with dementia and their family carers.

Carers mean RQ scores decreased over time, whereas those of the persons with dementia did not. Partner-rated RQ was the only factor positively influencing both persons with dementia and carer RQ baseline levels. Higher levels of carer stress negatively influenced baseline RQ scores among carers. Carer SOC and being a spouse were positively correlated with the baseline RQ scores of carers. Neuropsychiatric symptoms at baseline predicted a decline in carers' RQ over time, whereas carer social support and person with dementia unmet needs were associated with more positive RQ growth curves.

The LGM approach is invaluable in describing and explaining the development of RQ over time, offering the possibility of analysing change at the individual level and identifying influencing factors. LGM capitalises on both aspects of change over time (mean trend and individual departures from the mean trend). This combination of individual and group levels of analysis is unique. In this study, the significant mean and

variance of the intercept factor indicated a considerable between-person variation in the initial levels of perceived RQ for both persons with dementia and carers. To the best of our knowledge, this is the first study using LGM to evaluate RQ in dementia. However, findings from reviews of qualitative studies demonstrated the importance of exploring the heterogeneity of individual experiences to provide a richer understanding of RQ.^{12,43}

The decreasing carer RQ scores and the stable scores of person with dementia are in line with other studies.^{9–11} Although family carers may try to maintain their previous RQ¹², the caring process can be overwhelming and this may lead to the observed reduction in RQ.^{43,44} In this study, carer stress negatively influenced baseline carer RQ scores, as in our previous baseline analysis¹³ and in several other studies,^{10,11} although the direction of causation remains uncertain.

Social support emerged as a significant protector of carer RQ growth trajectories. This is in line with previous evidence that informal support mechanisms may reduce the burden of caregiving⁴⁵ and impact positively on RQ. A study with carers of people with young-onset dementia⁹ showed an association between ‘seeking social support’ and lower RQ. The authors suggested this might be due to reverse causality. Spouses perceiving RQ as low might seek more social support from relatives or friends, using emotion-focused coping. Our results extend the findings from a meta-analysis that called for interventions that enhance carers’ perceived social support, to prevent or alleviate subjective burden.⁴⁵ The authors called, specifically, for interventions resulting in carers ‘feeling connected’ rather than on ‘building connections’, since perceived social support was more strongly related to subjective burden than was the amount of social support actually received.⁴⁵ These interventions are even more relevant given the impact of COVID-19 restrictions on informal support mechanisms and social support services increasing social isolation and carer stress.^{46,47}

The positive association between carer SOC and the initial RQ level also supports our previous baseline analysis.¹³ Living in a satisfactory relationship may contribute to maintain or increase one’s SOC. Continuing home care does not necessarily decrease SOC and positive caregiving experiences may contribute to increasing SOC.⁴⁸ On the other hand, a stronger SOC, as a dispositional orientation, potentially protects family carers from psychological distress and may reduce the negative impact of caregiving.^{49–52} In a longitudinal study, SOC appears to buffer the impact of carer strain on symptoms of depression and anxiety in informal carers.⁵² This possible reciprocal association merits study, given previous findings outside caregiving contexts,^{53,54} and the potential for preventive interventions, namely targeting spouse carers with low SOC who seem to be a vulnerable group.^{51,55}

Being a spouse/partner (compared to adult child carer) emerged as a potential protector of initial carers’ RQ but did not influence RQ trajectories over time. A systematic review found little attention accorded to characteristics such as kin-relationship of the carer that could influence RQ perceptions.⁴ In one study, using a different relationship

index, partner carers reported a worse relationship with the person with dementia than adult child carers or children-in-law.⁵⁶ In contrast, in our previous baseline analysis, using a variable-centred approach (regression), findings showed that being a spouse/partner was positively associated with RQ, as rated either by the carer or the person with dementia.¹³ However, the current analysis, indicated that being a spouse/partner, as a potentially protective variable, loses explanatory power in the various RQ trajectories. The experience of giving and receiving care usually occurs within long-standing relationships which precede the onset of dementia and continue to evolve as it progresses. Providing support to spouses to come to terms with factors that menace their sense of couplehood might help them to adopt a more positive attitude toward their relationship and improve the RQ and care.^{57,58} Aspects of prior relationship influence caregiving dynamics and on how the caregiver and care-receiver roles are experienced.⁵⁹ Concurrently, the experience of living with dementia impacts on the relationship, often causing change or loss to which it is difficult to accept or adjust.⁶⁰

Higher baseline neuropsychiatric symptoms were associated with subsequent decline in RQ. Our analyses broaden the findings of a systematic review that suggested a weak association between relationship factors and challenging behaviours in dementia.⁷ However, most of the studies reviewed used a cross-sectional design and only assessed carers' RQ perspective.⁷ A recent longitudinal study with spouses of people with young-onset dementia found that lower perceived RQ was also associated with longer symptom duration, namely higher levels of apathy and hyperactivity.⁹ Other authors concluded that RQ moderated family carers' distress responses to daily neuropsychiatric symptoms.⁶¹

The extent of person with dementia unmet needs, as assessed at baseline by the researcher, were also linked with a positive trajectory in carers' RQ. The reasons for this are unclear and require further exploration e.g. as to whether specific domains of unmet needs impact on RQ, or whether the extent to which these needs are subsequently met is important.

Our study showed the significant reciprocal partner effect of the perception of the current RQ on the other member of the dyad. This underlines the importance of considering the perspectives of both the carer and the person with dementia and enabling each to maintain positive perceptions of RQ.

Identifying baseline determinants of RQ trajectories is helpful to develop timely interventions improving the development of health and QoL outcomes later. RQ is a key component of QoL.⁵⁻⁷ Understanding RQ and its influencing factors better will assist professionals in identifying how to promote QoL in dementia, namely by targeting risk factors that are amenable to intervention (e.g. neuropsychiatric symptoms, lack of social support). Hence, it can help researchers and policymakers to focus on those especially at risk. The interindividual differences at baseline, potentially influencing outcomes, suggest that further analyses could help to delineate those people with dementia and

family carers most at risk of developing negative RQ trajectories. Identifying and tracking individuals at risk of pursuing worse RQ trajectories is even more relevant in light of restrictions such as the recent COVID-19 lockdown that are especially challenging for those with poor RQ.⁶² As the COVID-19 pandemic and its effects continue, more research is needed to understand its impact on RQ.

Strengths and limitations

The study had several strengths. We used a longitudinal design, with repeated assessments, to analyse how relationship quality changes over time in a large, typical sample from eight countries, in different European regions. Furthermore, we were able to consider an extensive range of possible predictors of RQ longitudinally, with a potential to impact positively upon the QoL of persons with dementia and families. The LGM model, positioned at the intersection of variable- and person-centered analysis, allowed identification of intraindividual and interindividual differences and examined the effect of predictors on RQ change.

The study also had limitations. First, the sample may not be fully representative, limiting generalizability. Attrition from the baseline sample inevitably leads to some selection bias, with included people with dementia likely to be younger and less severely impaired, with carers having lower stress levels. Second, the follow-up period was 12 months; a longer follow-up period could have shown different trajectory patterns of RQ. Third, we only considered the baseline measurements of the potential predictors like stress and social support, rather than change over time. Finally, we did not consider the influence of a variety of potentially important factors including notably the RQ prior to the onset of dementia.

CONCLUSION

The present study offers novel insights into the course of RQ using a longitudinal design supported by LGM, a statistical method that considers intra- and inter-individual aspects. Tackling influencing factors such as carer-perceived social support, sense of coherence and person with dementia neuropsychiatric symptoms may help maintaining a good RQ trajectory, especially among more vulnerable dyads. These findings show the reciprocity between carer and person with dementia RQ and provide social and healthcare professionals with a preliminary understanding of RQ trajectory patterns and determinants across one year.

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CHAPTER 5

INTERACTION OF CAREGIVER-EXPRESSED EMOTIONS AND NEUROPSYCHIATRIC SYMPTOMS IN PERSONS WITH DEMENTIA: A LONGITUDINAL COHORT STUDY

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ABSTRACT

Objectives

Neuropsychiatric symptoms (NPS) have a major impact in persons with dementia (PwD). The interaction between the caregiver and the person with dementia may be related to the emergence of NPS. The concept of expressed emotions (EE) is used to capture this dyadic interaction. The aim of the present study is to examine longitudinally the association between EE in caregivers and NPS in PwD living at home.

Design

A longitudinal cohort study with 2 years of follow-up.

Setting

PwD and their informal caregivers living at home in the south of the Netherlands.

Participants

112 dyads of PwD and their caregivers from the MAAstricht Study of BEhavior in Dementia (MAASBED).

Main outcome measures

EE was measured at baseline with the Five-Minute Speech Sample (FMSS) and was used to classify caregivers in a low- or high-EE group. Associations between EE and neuropsychiatric subsyndromes (hyperactivity, mood and psychosis) measured with the neuropsychiatric inventory (NPI) were analysed over time.

Results

Seventy-six (67.9%) caregivers were classified in the low-EE group and 36 (32.1%) in the high-EE group. There was no difference between the EE groups in mean NPI scores over time. In the high-EE group, hyperactivity occurred more frequently than in the low-EE group at baseline ($p=0.013$) and at the other time points, but the mean difference was not always significant. There were no differences for the mood and psychosis subsyndromes. PwD with caregivers scoring high on the EE subcategory critical comments had an increased risk of institutionalisation (OR 6.07 (95% CI 1.14-32.14, $p=0.034$)) in comparison with caregivers scoring low on critical comments.

Conclusions

High EE in informal caregivers is associated with hyperactivity symptoms in PwD. This association is likely to be bidirectional. Future studies investigating this association and possible interventions to reduce EE are needed.

INTRODUCTION

Neuropsychiatric symptoms (NPS), such as a depressive mood and agitation, are a major problem in persons with dementia (PwD). They may have several negative effects for the person with dementia and result in a loss of quality of life.^{1,2} NPS may also have a great impact on the family caregiver of the person with dementia and lead to an increased burden and negative health effects.³ NPS are also important determinants for nursing home placement.⁴ NPS are associated with patient-related factors such as age, sex and comorbidity.^{5,6} However, the psychosocial environment, such as interpersonal interactions between the caregiver and the person with dementia, may also influence the behaviour of the person with dementia. One of the concepts that has been developed to capture interpersonal interaction is expressed emotion (EE).

The construct of EE was developed by Brown et al. and used in multiple studies to investigate the associations between relapses in patients with schizophrenia and the interactions between these patients and their relatives.⁷ A commonly used definition of EE is given in an overview of Hooley from 2007: ‘expressed emotion is a measure of how much criticism, hostility, or emotional overinvolvement (EOI) the caregiver expresses when speaking about a person with psychopathology’.⁸ Caregivers expressing a more-than-usual amount of criticism, hostility or EOI are generally classified as having high EE levels. The concept of EE has also been studied in PwD and their caregivers.⁹ Several studies have focussed on caregiver well-being and found a high EE was related to several negative effects in caregivers, such as depression and distress.^{10,11} There are also several studies suggesting a link between high EE and negative effects for PwD.¹² The interaction mechanisms between PwD and their caregivers are complex.⁹ According to the ecological model of Lawton¹³, PwD are more vulnerable to the demands of their psychosocial environment because of their decreased competences, which may lead to behavioural problems if the demands of the environment exceed those of the person and their abilities. For example, due to the dementia (verbal) communication may become affected, unmet needs may arise and result in behavioural challenges if those around the person cannot meet those needs. This requires a great deal of flexibility from the caregiver. Caregivers that are less flexible and more self-critical are thought to project this to the PwD.⁹ In line with this, a recent study in Hong Kong showed that the negative impact of NPS on outcomes in dementia caregivers was mediated by EE.¹⁴ Another study found that daughters who believe that their parent’s behaviour was within the control of that parent were more likely to exhibit high EE¹⁵, and they suggest that educating these daughters may help reduce stress.

However, a systematic review did not find any consistent effects of relationship factors such as EE on outcomes such as institutionalization and quality of life in PwD.¹² They did find an association between relationship quality and global challenging behaviour, though the evidence was weak. The methodological quality of the included studies was

assessed as poor (e.g., risk of confounding, small sample sizes, and no reporting of effect sizes).

The available literature questions whether EE is a state-like or trait-like characteristic. Overall, it is assumed that a ‘dual-identities model’ of both state and trait-like features is most likely: some caregivers will always show a higher EE compared to others, but the level of EE can change over time⁹ and might therefore be modifiable. For example, a vulnerable caregiver might have a high EE even when there is not a significant amount of stress. On the other hand, a caregiver that is quite resilient will only show high EE behaviour with multiple serious stressors. It is important to know which factors can influence EE. A recent study in caregivers of patients with Alzheimer’s disease found that depressive temperament traits might predict higher levels of EE.¹⁶

To identify possible targets for interventions to reduce NPS, it is important to have a better understanding of the association between EE and NPS. Furthermore, it is important to investigate whether this interaction is indeed modifiable and thus if it is related to stable and/or influenceable characteristics of the caregiver. The aim of the present study is to examine the association between EE in informal caregivers and NPS in PwD living at home. Data from a longitudinal cohort study¹⁷ were used to (1) examine a possible association between baseline EE in caregivers and NPS in PwD at baseline and over time; (2) explore factors associated with EE; (3) examine the association between EE and institutionalization rate; and (4) examine the impact of EE on caregiver functioning. It is hypothesized that high EE is related to higher levels of NPS in PwD, higher risk of institutionalization and more negative effects in caregivers.

METHODS

Subjects

The present study uses data from the MAAstricht Study of BEhavior in Dementia (MAASBED). MAASBED is a 2-year follow-up study focussing on the course and risk factors of NPS in dementia.¹⁷ Dyads of patients and their caregivers were recruited at the Memory Clinic of the Maastricht University Medical Center or the geriatric division of the Community Mental Health Care (RIAGG), Maastricht, the Netherlands. PwD were included if they met the DSM-IV criteria for dementia¹⁸, were outpatients, and had a reliable informant. Caregivers were included if they were the primary caregiver and had contact with the patient at least once a week. At baseline, all PwD were living at home. Written informed consent was obtained from all subjects. The study was approved by The Medical Ethics Committee of the University Hospital Maastricht.

PwD measures

General characteristics such as age, sex, dementia type, time of diagnosis and

educational background were collected. Cognitive functioning was measured with the Mini Mental State Examination (MMSE).¹⁹ Patient dependency with regard to daily activities was measured with the Interview for Deterioration in Daily living activities in Dementia (IDDD).²⁰ Furthermore, the severity of dementia was measured with the Global Deterioration Scale (GDS).²¹ Data about psychotropic medication use (antidepressants, antipsychotics and benzodiazepines) was collected summarily.

NPS were measured with the Neuropsychiatric Inventory (NPI).²² The NPI is a structured interview with the caregiver that measures NPS in 12 domains: delusions, hallucinations, depression/dysphoria, aggression/agitation, fear, euphoria, apathy, disinhibited behaviour, liability, repetitive behaviour, sleeping problems, and change of eating patterns. The scoring in each domain is obtained by multiplying the severity (1 'mild' to 3 'severe') by the frequency (1 'sometimes' to 4 'very often'). A previous factor analysis of the NPI identified three behavioural subsyndromes: mood/apathy, psychosis, and hyperactivity, with anxiety as a separate syndrome.²³ Total scores for each subsyndrome were computed as the sum of observed NPI item scores for each factor.

Measurements were carried out every six months. If a person with dementia was admitted to a nursing home during the 2-year follow-up, data were still collected for the next follow-up time after admission.

Caregiver measures

General characteristics such as sex, age, educational level, kinship type and number of contact hours with the person with dementia were collected. Expressed emotion was assessed by the Five-Minute Speech Sample (FMSS).²⁴ The FMSS is a non-time-consuming method to assess EE: caregivers are asked to speak without interruption for five minutes, describing their relative and how they get along together. The speech samples are audiotaped and transcribed. The number of critical comments, the amount of emotional overinvolvement (EOI), the initial statement, and the relationship between patient and caregiver are rated. In this study, two trained and qualified raters coded the transcripts using the guidelines described for coding EE. In order to assess the inter-rater reliability, twelve interviews were randomly selected and rated by two other highly experienced blind raters to assess reliability and consistency. The inter-rater reliability between these highly experienced raters and the two qualified raters was 100%. Caregivers were classified as 'high-EE' if they scored on the critical scale and/or on the EOI scale, and otherwise they were rated as 'low-EE', according to the method described by Magana et al.²⁴ In the low-EE group, caregivers were rated as 'borderline EOI' or 'borderline critical' if there were some indications for a high EE score but not enough to fulfil the high EE criteria.

For each of the 12 neuropsychiatric symptoms on the NPI, caregivers rated the level of distress they experienced on a scale from 0 (none) to 5 (extreme). The NPI-Distress score is the sum of these 12 ratings (range 0-60).²²

Caregiver subjective competence was measured with the Short Sense of Competence Questionnaire (SSCQ).²⁵ This questionnaire consists of 7 items rated on a 5-point scale (1 “agree very strongly” to 5 “disagree very strongly”; range 7-35). These items reflect three domains of caregivers’ feelings of being capable of caring for a person with dementia: (a) satisfaction with the person with dementia as a recipient of care; (b) satisfaction with one’s own performance as a caregiver; and (c) consequences of involvement in care for the personal life of the caregiver.

Depressive symptoms were measured with the Montgomery-Asberg Depression Rating Scale (MADRS) 22, a structured interview administered by the clinician. Ratings (from 0 to 6) on 10 items were summed (range 0-60).²⁶ Personality traits were assessed with the NEO-Five Factor Inventory (NEO-FFI).²⁷ The NEO Five-Factor Inventory (NEO-FFI) is a shortened version of the NEO Personality Inventory-Revised.²⁷

Statistical analyses

Demographic and clinical characteristics of the patients and the caregivers were calculated as means with standard deviations (SD) or as frequencies for categorical data. To examine baseline differences (in the characteristics of the patient and caregiver) between the low- and high-EE groups, the independent-samples t-test, linear regression and χ^2 test were used. Square root transformations were used to normalise distributions if necessary (for NPI scores) for statistical tests, the data itself is represented in their raw form (e.g. means) for a better understanding of the data. Spearman’s correlations were used to explore the pairwise relationships between the PwD variables and the caregiver variables, see supplementary table 1 and 2.

Linear mixed models tested the association between EE and change in NPI scores over time. The models included a random intercept and random slope with an unstructured correlation matrix. An interaction term between EE and time was included, and analyses were adjusted for the age and sex of the PwD and MMSE score. Logistic regressions were used to investigate possible associations between EE group and binary outcome variables such as institutionalization. Additionally, the high-EE group was subdivided into a critical and an EOI group, and comparisons were made of critical vs. not critical and high in EOI vs. not high in EOI. Independent samples t-test was used to explore differences between personality traits and EE groups.

All analyses were done in Stata/SE 12.1 (StataCorp, TX), and the level of statistical significance was $p < 0.05$ in two-sided tests.

Patients and public involvement statement

No patients and/or public were involved.

RESULTS

Baseline characteristics

Of the 119 informal caregivers participating in MAASBED, 112 (94.1%) agreed to be interviewed at baseline. Therefore, a total of 112 dyads of PwD and their caregivers were included in the analysis. Caregivers who participated did not differ from those who did not participate in terms of age, sex, education, or depressive symptoms, nor did the respective patients in terms of dementia severity or NPS. During the 2-year follow-up, 47 dyads were lost to follow-up because of refusal ($n=21$) or death ($n=26$), see supplementary figure 1. Caregivers and PwD lost to follow-up did not differ from those who did not in terms of sex (caregiver and PwD), age of the PwD, total NPI scores or EE-group; but caregivers lost to follow-up were relatively older compared to caregivers not lost to follow-up (67.7 vs. 61.4, $p=0.003$), and more PwD had a GDS score of 5 or 6 ($p=0.032$).

The PwD had a mean age of 78.7 (SD = 8.3, range 56-99), and 66 (58.9%) were women. Eighty-four PwD (75.0%) had Alzheimer's disease, 19 (17.0%) vascular dementia, 2 (1.8%) fronto-temporal dementia, 3 (2.7%) Parkinson's disease, 1 (0.9%) primary progressive aphasia (PPA) and 3 (2.7%) mixed dementia. The mean duration of illness was 42.3 months (SD = 30.4, range 6- 120), and the mean MMSE score was 18.1 (SD = 4.7). Concerning the GDS score, 17.9% having stage 3 cognitive functioning, 53.6% stage 4, 27.7% stage 5 and 0.9% stage 6.

The mean age of the caregivers was 63.5 years (SD = 12.2, range 36-90), 74 (66.1%) were women, 58 (51.7%) were spouses, 46 (41.1%) were children, and 8 (7.1%) had another relationship (e.g., close friends). The mean duration of care was 27.9 months (SD = 26.1, range 3-120), and the caregivers spent a mean of 92.8 contact hours per week (SD = 70.8, range 2- 168) with the PwD.

Expressed emotion and baseline group differences

Seventy-six (67.9%) caregivers were classified in the low-EE group, and 36 (32.1%) caregivers were classified in the high-EE group. In the high-EE group, 19 caregivers scored on critical comments, 11 caregivers were emotionally overinvolved, and 6 caregivers were both critical and emotionally overinvolved. In the low-EE group, 12 caregivers were borderline-critical, and 9 caregivers were borderline-emotionally overinvolved.

There were no differences between the high- and low-EE groups in caregiver age, sex or kind of relationship with the patient (Table 1). The caregivers in the low-EE group had a higher educational level. In addition, there were no differences between the high and low-EE groups in patient age, sex, disease severity, cognitive status or disease duration (Table 2).

Table 1. High-EE versus low-EE: caregiver characteristics

	Low-EE N = 76	High-EE N = 36	P-value
Relationship			0.336
- Spouse	43	15	
- Son/daughter	28	18	
- Other	5	3	
Gender female (%)	47 (61.8%)	27 (75%)	0.170
Age (SD)	64.7 (1.5)	60.9 (1.7)	0.129
Educational level			0.024
- Low	40	27	
- High	36	9	
Contact hours per week			0.083
- <50 h/week	27	19	
- >50 h/week	49	17	
MADRS (SD)	8.0 (6.1)	9.0 (6.8)	0.44
SSCQ (SD)	24.8 (5.7)	21.1 (6.1)	0.003

Abbreviations: EE, expressed emotion; MADRS, Montgomery-Asberg Depression Rating Scale; SSCQ, Short Sense of Competence Questionnaire.

Expressed emotion as predictor of neuropsychiatric symptoms at baseline

There was a six-point difference between the EE groups in mean baseline NPI score, but this difference was not statistically significant (low EE: 20.1, high EE: 26.1, $p=0.241$). Analyses were repeated for the three behavioural subsyndromes to examine differences in mood/apathy, hyperactivity, and psychosis. In the high-EE group, the mean hyperactivity scores were higher than those in the low-EE group (10.3 vs. 5.4, $p=0.021$), but this was not the case for the mood or psychosis subsyndrome (9.2 vs. 8.6, $p=0.943$ and 3.9 vs. 4.1, $p=0.748$, respectively). Hyperactivity also showed a significant result when correcting for PwD age, sex and MMSE score ($p=0.013$).

Table 2. High-EE versus low-EE: patient characteristics

	Low-EE N = 76	High-EE N = 36	P-value
Gender female (%)	44 (57.9%)	22 (61.1%)	0.747
Age (SD)	78.6 (8.4)	78.7 (8.4)	0.977
GDS			0.761
- stage 3	15	5	
- stage 4	39	21	
- stage 5	21	10	
- stage 6	1	0	
MMSE (SD)	17.8 (4.7)	18.7 (4.5)	0.325
Disease duration, months (SD)	39.8 (30.0)	47.5 (31.1)	0.214
NPI score (SD)	20.1 (20.2)	26.1 (26.0)	0.241
IDDD-initiative	22.9 (9.7)	21.6 (9.9)	0.519
IDDD-performance	19.8 (10.9)	19.9 (10.6)	0.968
Psychotropic medication			
Antidepressants	17 (22.4 %)	13 (36.1 %)	0.125
Antipsychotics	8 (10.5%)	3 (8.3%)	0.716
Benzodiazepines	19 (25%)	7 (19.4%)	0.515

Abbreviations: EE, expressed emotion; GDS, Global deterioration scale; IDDD, Interview for Deterioration in Daily living activities in Dementia; MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory.

Expressed emotion as predictor of neuropsychiatric symptoms over time

Performing regression analyses for the three behavioural subsyndromes per time point showed higher mean scores for the hyperactivity symptoms in the high-EE group compared to the low-EE group (Figure 1). However, not all mean scores differed significantly at each time point when correcting for PwD age, sex and MMSE score: on baseline $p=0.013$, on T1 $p=0.003$, on T2 $p=0.913$, on T3 $p=0.099$ and on T4 $p=0.838$.

Analyses were also repeated for caregivers who scored high on critical comments compared to caregivers scoring low on critical comments, and the results showed higher mean scores for hyperactivity symptoms over time in the 'critical' group (Figure 2). At all time points except for T2 and T4, scores differed significantly when correcting for PwD age, sex and MMSE score: on baseline $p=0.002$, on T1 $p<0.001$, on T2 $p=0.217$, on T3 $p=0.007$ and on T4 $p=0.616$. There was no significant difference between the high-EOI group and the low-EOI group.

Linear mixed models showed no associations between EE groups and the change in NPI scores over time, also not when repeating the analyses for the subsyndromes. There was also no significant time-by-group interaction effect.

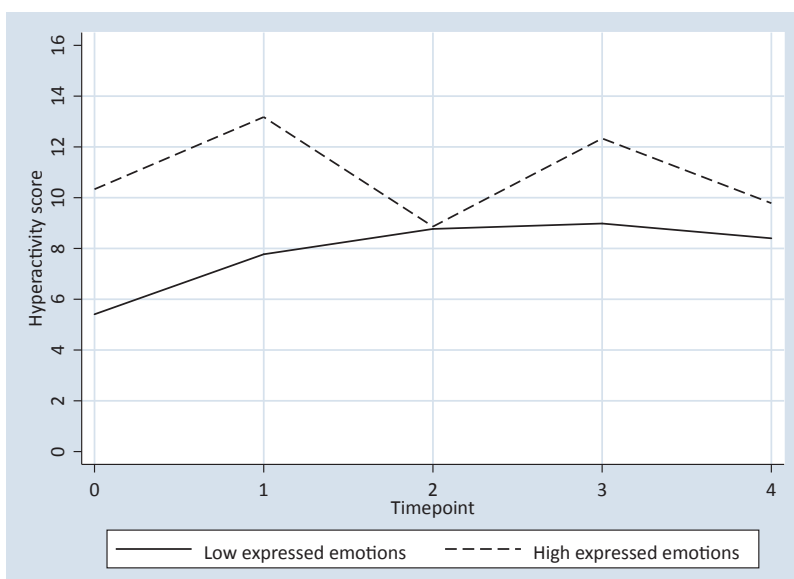


Figure 1: Mean hyperactivity score on the NPI by EE-group

Expressed emotion and institutionalisation

PwD with caregivers in the high-EE group had a higher risk of admission to a nursing home (OR 3.74 (95% CI 1.01-13.87, $p = 0.048$, corrected for PwD age, sex and MMSE

score)). When comparing caregivers scoring high on critical comments *versus* caregivers scoring low on critical comments, the risk increased (OR 6.07 (95% CI 1.14-32.14, $p=0.034$, corrected for PwD age, sex and MMSE score)). Correcting for IDDD instead of MMSE score, as well as also correcting for NPI-score, did not have a major impact on the results.

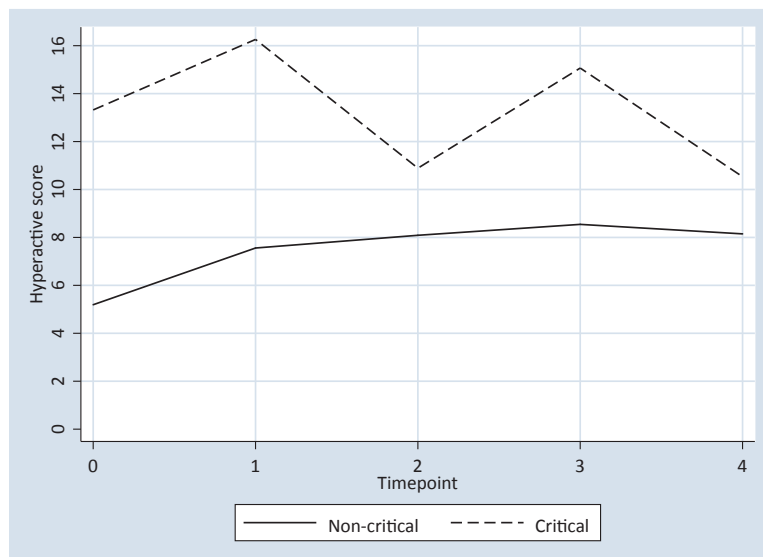


Figure 2: Mean hyperactivity score on the NPI by EE subgroups critical vs. non-critical

Exploring caregiver characteristics associated with low vs. high expressed emotions

Associations between caregiver personality traits assessed with the NEO-FFI and EE were explored. Mean scores on neuroticism were higher in the critical EE group than in the noncritical EE group (34.1 (SD 7.8) vs. 29.6 (SD 6.9), $p=0.015$), whereas other personality traits did not significantly differ. Also, caregiver subjective competence measured with the SSCQ differed between the two groups. Mean scores were higher in the low-EE group than in the high-EE group (24.8 (SD 5.7) vs. 21.1 (SD 6.1), $p=0.0026$). The difference was bigger comparing the noncritical EE group with the critical EE group (24.2 (7.1) vs. 19 (5.6), $p=0.001$).

There were no significant differences between EE groups in scores on MADRS. However, caregivers in the high-EE group reported significantly more distress on the NPI at baseline but not at the other follow-up moments. Caregivers scoring high on critical comments reported significantly more distress on the NPI at each time point (Table 3), except on T4.

Table 3. Mean scores on NPI distress

EE group	NPI distress (mean)				
	Baseline	T1	T2	T3	T4
EE: low vs. high	9.6 vs. 14.6 p = 0.015	11.7 vs. 16.1 p = 0.084	11.8 vs. 16.2 p = 0.079	10.5 vs. 17.4 p = 0.071	11.1 vs. 12.7 p = 0.71
Critical comments: low vs. high	9.6 vs. 16.1 p = 0.002	11.4 vs. 18.6 p = 0.011	11.5 vs. 19.4 p = 0.008	10.4 vs. 22.2 p = 0.009	10.3 vs. 14.7 p = 0.437

Abbreviations: EE, expressed emotion; NPI, Neuropsychiatric Inventory. Note: due to loss to follow-up and institutionalization numbers get smaller over time; T4 analyses are based on n=29 with n=6 in the high-EE group and n=3 in the high critical group.

DISCUSSION

The aim of the current study was to examine the association between EE in caregivers and neuropsychiatric symptoms in PwD living at home. Our results show that high levels of EE were present in 32.1% of the caregivers. High EE was related to more hyperactivity symptoms in PwD on the NPI. Scores were even higher in the high-critical-EE subgroup of caregivers. No associations were found between EE subgroups and mood/apathy or psychosis. PwD with caregivers who gave more critical comments were more likely to become institutionalised during the two-year follow-up.

The present study confirms previous studies and adds to the evidence that there is an association between interpersonal interaction and behaviour in the person with dementia.^{12,14,28} Hooley et al. described that it seems most likely that this direction is at least bidirectional⁸, it could be that our results fit this theory. Especially in dementia, where verbal communication may become affected, interactions may become more complex, and high EE may lead to negative interaction sequences. In this study, a higher number of critical comments was related to more hyperactivity symptoms. In the unmet-needs model of Cohen-Mansfield²⁹, problem behaviour such as hyperactivity is thought to arise from difficulties communicating one's needs. Caring for a person with dementia can be very difficult, time- and energy-consuming and frustrating, which may lead to a caregiver becoming exhausted and reacting frustratedly. High levels of criticism from the caregiver towards the person with dementia may result in an unsafe environment where the caregiver is not able to meet the needs of the person with dementia. As a result, the person with dementia may become irritated or offended with no ability to cope with critical comments or to react in a non-agitated verbal way. The association between critical comments and symptoms of hyperactivity such as agitation may be part of a more complex web of interactions between the caregiver and the person with dementia. This complex web is also highlighted by the fact that caregivers in the high EE group had a higher distress score on the NPI and reported lower caregiver competence measured with the SSCQ on baseline.

In this study, high EE was associated with the hyperactivity subsyndromes on the NPI but not with the subsyndromes mood/apathy and psychosis. However, we know

that symptoms other than hyperactivity also have an impact on caregiver functioning. For example, apathy is known to have a big impact on caregivers³⁰ and was found to be associated with deterioration of the relationship quality in a previous study using MAASBED³¹, but we did not find an association between apathy and high EE in the present study.

The present study indicates that EE is partly determined by the stable characteristics of the caregiver. First, caregivers in the low-EE group had a significantly higher educational level. Second, caregivers in the critical comment subgroup had higher scores on neuroticism. This is in line with an earlier study using MAASBED that found caregivers with a non-adapting strategy reported more patient hyperactivity than did caregivers who used a supporting strategy.³² Stable caregiver characteristics were thought to be important determinants of the caregiver management strategy. We also found caregiver distress related to neuropsychiatric symptoms, measured with the NPI, to be higher in caregivers in the critical comments group. This might be a possible target for intervention. The prevalence of NPS in PwD might be reduced when caregivers receive interventions designed to improve positive interactions with the PwD. Promoting an early and positive adaptation in the caregiver role and more leisure time for the caregiver might be important.^{33,34} Additionally, psychoeducation and teaching of effective coping strategies, such as seeking distraction, seeking social support, and fostering reassuring thoughts, might be effective in reducing negative responses to stressful events in daily life.³⁵ Reducing stigma, for example, by large-scale awareness campaigns, might reduce EE, since the caregiver's experience of stigma is found to be associated with high EE.³⁶ In the end, reducing EE might even delay patient institutionalisation.

The strengths of the present study are the relatively large sample size, the 2-year follow-up and the fact that confounding factors were taken into account. However, the study has some limitations. First, the FMSS is not the gold standard for measuring the level of EE. The FMSS has a tendency to underidentify high-EE relatives,³⁷ which could have masked the association between NPS and caregiver EE. However, in the context of this large study, it was not feasible to use a more extensive and time-consuming measure, such as the Camberwell Family Interview (CFI), which takes approximately 5 hours per person (interviewing and scoring).³⁷ Additionally, the level of EE was only assessed at baseline, so we could not study possible changes in EE over time. Therefore, we could only analyse the association with baseline EE and NPS over time, and we were not able to analyse whether EE changed during follow-up and the association of this possible change with NPS. It could be that EE changed significantly during follow-up and that this influenced NPS during follow-up. Future studies should include a follow-up of EE to further investigate whether EE is a stable characteristic. Another limitation might be that caregiver reports were used to assess NPS. Caregivers in the high-EE group might rate NPS more frequently and more severely. However, the finding that high EE was only associated with symptoms of hyperactivity and not with other NPS contradicts this

argument. Also, we did not have enough data of any psychosocial interventions during the study period, relationship quality of the dyad, caregiver strain and of the presence of other informal caregivers or community services. Future studies could include this to investigate whether these factors influence the interactions in the dyad or not. Also, it is important that future studies analyse the caregiver characteristics associated with low vs. high expressed emotions more extensively. Finally, it was notable that mean hyperactivity scores in the high EE group dropped on T2. Inspection of the data showed that this was due to measurements in 3 patients who went from a high hyperactivity score on T0 and T1 to a score of zero on T2 for unknown reasons. Leaving these measurements out of the analysis resulted in a mean difference in hyperactivity scores of 4.06 ($p = 0.043$).

CONCLUSION

In conclusion, high EE in caregivers is associated with more hyperactivity symptoms in PwD. In dementia care, it seems crucial to pay attention to interpersonal interactions between caregivers and PwD. Interactions between PwD and caregivers may be complex, but reducing caregiver EE may attenuate hyperactivity symptoms in PwD. Future intervention studies that focus on the empowerment of dyads or the support of caregivers in the context of dementia should consider including measures of EE to study if EE can be reduced and if this affects outcomes in the PwD, such as hyperactivity symptoms. Eventually, this could improve the quality of life of PwD and their caregivers and possibly also delay institutionalization.

FUNDING

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Spearman's correlations PwD factors

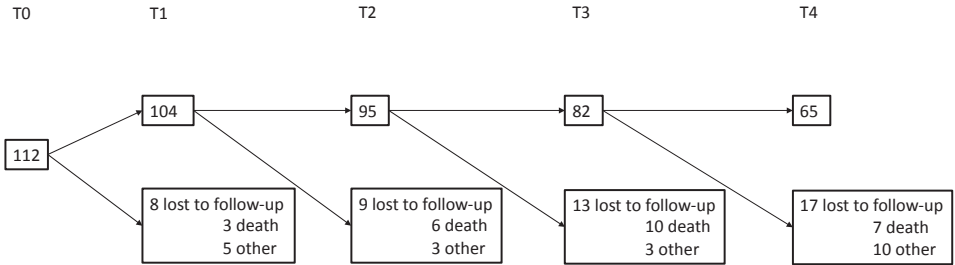
	MMSE	GDS	IDDD-i	IDDD-p	NPI	EE
MMSE	1.0					
GDS	-0.56 (<0.001)	1.0				
IDDD-i	0.25 (0.009)	-0.33 (<0.001)	1.0			
IDDD-p	-0.28 (0.002)	0.38 (<0.001)	-0.63 (<0.001)	1.0		
NPI	-0.09 (0.33)	0.17 (0.07)	-0.26 (0.007)	0.18 (0.05)	1.0	
EE	0.09 (0.33)	0.03 (0.79)	-0.06 (0.51)	0.0 (1.0)	0.14 (0.13)	1.0

Abbreviations: MMSE, Mini Mental State Examination. GDS, Global deterioration scale. IDDD-i, Interview for Deterioration in Daily living activities in Dementia, initiative subscale. IDDD-p, Interview for Deterioration in Daily living activities in Dementia, performance subscale. NPI, Neuropsychiatric Inventory. EE, expressed emotion.

Supplementary Table 2. Spearman's correlations caregiver factors

	NPI-D	SSCQ	MADRS	NEO-FFI-n	EE
NPI-D	1.0				
SSCQ	-0.53 (<0.001)	1.0			
MADRS	0.38 (<0.001)	-0.38 (<0.001)	1.0		
NEO-FFI-n	0.35 (<0.001)	-0.43 (<0.001)	0.68 (<0.001)	1.0	
EE	0.21 (0.04)	-0.27 (0.007)	0.10 (0.34)	0.09 (0.40)	1.0

Abbreviations: NPI-D, Neuropsychiatric Inventory-Distress score. SSCQ, Short Sense of Competence Questionnaire. MADRS, Montgomery-Asberg Depression Rating Scale. NEO-FFI-n, NEO-Five Factor Inventory, neuroticism item. EE, expressed emotions.



Supplementary Figure 1. Lost to follow-up

CHAPTER 6

IMPORTANCE OF SOCIAL SUPPORT WITHIN THE NURSING TEAM ON AGITATION IN RESIDENTS WITH DEMENTIA

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ABSTRACT

Background

Neuropsychiatric symptoms (NPS) are very common in residents with dementia. While patient-related factors and physical environmental factors have been associated with the presence and severity of neuropsychiatric symptoms, the influence of the nurses' demographic and job characteristics on NPS is less well known.

Objectives

The aim of this study was to explore the association between the job characteristics of the nursing team and the prevalence and severity of agitation in residents with dementia.

Design

Cross-sectional study.

Setting: Three nursing home organizations in the south of the Netherlands.

Participants

A total of 182 residents from 22 dementia care units aged ≥ 65 years and having a diagnosis of dementia.

Measurements

The primary outcome measure was agitation measured with the Cohen-Mansfield Agitation Inventory (CMAI). An online questionnaire was used to gather demographic information and job characteristics of the nursing team.

Results

Nurses' level of social support within the team was significantly associated with physical aggression in patients ($p=0.006$, OR 0.88 (95%CI 0.81 – 0.96)) with a higher score on social support being associated with a lower chance of physical aggression. Other job characteristics were not significantly associated with physical aggression, non-aggressive physical agitation and verbal agitation.

Conclusion

Higher scores of social support within the nursing team were associated with a lower prevalence of physical aggression measured with the CMAI. Longitudinal, large-scale, studies are needed to study the direction of this association. Interventions aimed at improving social support may lead to less physical aggression in residents with dementia or a better coping with aggression.

INTRODUCTION

Neuropsychiatric symptoms (NPS) are very common in residents with dementia. A systematic review revealed that a particular high prevalence is found for agitation, with at least one agitation symptom being present in 79% of people with dementia as measured with the Cohen-Mansfield Agitation Inventory (CMAI).¹ NPS may lead to profound negative effects for the resident with dementia, including reduced quality of life^{2,3}, and cause distress in other residents and nursing staff.⁴ NPS, and agitation in particular, may lead to an increased prescription of psychotropic drugs⁵, which may be inefficient and lead to harmful side-effects such as falling.⁶

Several factors are known or thought to be associated with NPS in dementia. These factors can be divided into patient-related factors and environment-related factors, and the environment-related factors can subsequently be divided into physical environmental and psychosocial environmental factors. Patient-related factors such as gender and severity of dementia are known to be associated with NPS.^{7,8} Zuidema et al. found that patient-related factors insufficiently explained differences in the prevalence of NPS between dementia care units, therefore suggesting an influence of the environment.⁹ Physical environmental factors associated with the prevalence of NPS are for example related to the building induced perception of privacy^{10,11}, temperature¹² and the number of residents per unit, although the positive effect of small-scale living facilities on behavior has not been proven.¹³ Also, the right amount of sensory stimulation and a non-institutional design are associated with less NPS.^{14,15}

In contrast to research into the relation of patient-related factors and physical environmental factors, research is less extensive and conclusive about the association between psychosocial environment and NPS. The psychosocial environmental factors can be divided in factors on a unit level and factors on an individual nurse level. On the unit level, factors such as staffing levels (e.g. number of residents per registered nurse) are associated with NPS. For example, whether nurses perceive staffing levels as adequate is associated with the amount of aggressive behavior.^{16,17} Also, the presence of a role model, social support within the nursing team and working climate may be associated with NPS. For example, one study found that caregivers experienced a less positive working climate in wards with a relatively high prevalence of violence.¹⁷ Concerning the individual nurse level, a study in informal caregivers found that caregiver management strategies are associated with the presence of neuropsychiatric symptoms in patients with dementia.¹⁸ These management strategies were, at least partly, determined by caregiver characteristics such as gender, education and personality. Related to professional caregivers, i.e. nurses, their characteristics may also influence their management strategies and they may be associated with the prevalence and severity of NPS. In other words, the way a nurse fulfils her/his job may possibly increase or decrease the risk of aggressive behaviour.¹⁹

In addition to characteristics such as gender, personality, age and working experience, also the way professional caregivers experience their job may be related to NPS. Important for the way professional caregivers experience their job are job characteristics such as job demands, job control and social support within the workplace as described by Karasek et al. in the Job Demands-Control-Support model.^{20,21} This model suggests that the combination of high job demands and low job control results in high job strain. This may in turn lead to negative effects on patient outcomes. For example, one study found that in dementia care units where nursing staff reported high job strain, the prevalence of NPS was significantly higher compared to units where nursing staff reported low job strain.²² Another study found that a higher psychological workload and a lower job satisfaction were associated with a higher prevalence of violence.¹⁷ Also high job demands in combination with high job control seem to decrease the risk of a possible consequence of NPS, namely the use of antipsychotics.²³ Furthermore staff stress is associated with psychotropic drug use in residents with dementia.⁵ Johnson & Hall added the 'protective' effect of high social support within the workplace to the Job Demands-Control-Support model.²⁰ Higher scores on social support predict higher job satisfaction and lower social support scores may lead to more psychosomatic health complaints in nurses.²⁴ Moreover, social support from co-workers or supervisors may help to cope with a high workload²⁴ and possibly increase resilience to cope with adverse events such as agitated behaviour in patients.

In summary, quite some research has been done on the association of patient-related factors and physical environmental factors on agitation in residents with dementia, but less emphasis has been placed on the association with psychosocial environmental factors especially social support within the nursing team and the job characteristics of the individual nurse. Therefore, the aim of this study is to explore the relation between nurses' demographics and job characteristics and the prevalence and severity of agitation in residents with dementia. Agitation is chosen because it is known to cause the greatest distress in nursing staff.⁴ It is hypothesized that less working experience, lower perceived job autonomy and satisfaction, lower social support of supervisors and co-workers, and burnout symptoms are related to a higher score on agitation measured with the CMAI.

METHODS

Design and subjects

This cross-sectional study is part of a study called the Nursing home Environment Study of Behavior in Dementia (NESBED). Nursing home residents were recruited from three nursing home organisations in the south of the Netherlands comprising 22 dementia care units. Both small (on average seven residents) and large-scale units (on average 20 residents) were included. Subjects were included if they fulfilled the following criteria:

- 65 years or older,

- Having a diagnosis of dementia based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition²⁵,
- Complete data on baseline.

All professional caregivers (registered nurses and nursing-assistants) that were willing to participate were included with the exception of volunteers.

The medical ethical committee of the Academic Hospital Maastricht has approved the design of the study (MEC 10-4-038). Professional caregivers and residents gave their informed consent before inclusion. For all residents the legal representatives also gave written informed consent.

Assessments residents

Resident characteristics and measurements were assessed with instruments filled in by the nursing staff, which was specially trained in the specific measurement instruments. In order to prevent nursing staff members influencing each other and support privacy when filling in the work-related questionnaires, each nursing staff member was able to fill out the questionnaires on a website at a time and place convenient for him or her.

The primary outcome measure was agitation measured with the Cohen Mansfield Agitation Inventory (CMAI).²⁶ The CMAI is an instrument that assesses 29 items concerning agitated behavior, examples of items are: 'Kicking', 'Throwing things', 'Pace, aimless wandering' and 'Repetitive sentences or questions'. Each Likert-type item has a maximum score of 7 ranging from 'never' to 'several times per hour'. The total score sums the individual items and ranges from 29 to 203. The scale has been validated and translated into Dutch, with good internal consistency (Cronbach's alpha of 0.82) and interrater agreement for the total score (Cohen's kappa of 0.89).²⁷

Cognitive functioning was measured by the Mini Mental State Examination (MMSE)²⁸ or with the Severe Impairment Battery (SIB) in case of severe cognitive impairment.²⁹ The severity of dementia was assessed with the Global Deterioration Scale (GDS).³⁰ The GDS has 7 stages, ranging from 'no cognitive decline' to 'very severe cognitive decline'.

Assessments nursing team

An online questionnaire was used to gather demographic information, such as gender, age, years of working experience and marital state of the individual nurses. Job characteristics were measured by items of the following questionnaires:

- The Maastricht Autonomy Scale³¹ to measure job autonomy (7 relevant items selected, scoring ranging from 0 'very little' to 4 'very much': 'determine method of working yourself', 'leave workplace when wanted', 'determine work goals yourself', 'determine order of work yourself', 'evaluate work yourself', 'pause work when wanted', 'determine amount of work to be done during a certain period yourself'). The scale is considered to have an acceptable validity and reliability.³¹ Cronbach's alpha in the present study was 0.81.

- The Dutch version of the social support scale of the Job Content Questionnaire^{32,33} to measure social support by the supervisor and co-workers in the work place (8 items ranging from 1 'strongly disagree' to 4 'strongly agree': 'supervisor concerned', 'supervisor pays attention', 'helpful supervisor', 'supervisor good organizer', 'coworkers competent', 'coworkers interested in me', 'friendly coworkers', 'coworkers helpful'). The reliability is good³², Cronbach's alpha in this study was 0.80.
- The Utrecht Burn-Out Scale (UBOS)³⁴ to measure the degree of possible burnout symptoms (5 relevant items selected ranging from 0 'never' to 6 'every day': 'emotionally drained from work', 'feeling used up at end of a working day', 'feeling tired when getting up in the morning and facing another working day', 'working with people whole day is a strain', 'feeling burned out from work'). The scale has been validated.³⁵ Cronbach's alpha in the present study was 0.71.
- Several items concerning job demands ('working under pressure of time', 'peaks in the work', 'staff have to work too hard', 'too much work has to be done', 'too little time to finish the work', 'pace of work is too high', 'work is mentally exacting', 'work is too complicated') and job satisfaction as previously described by De Jonge.³¹ Cronbach's alpha concerning the job demands in the present study was 0.86.

Analysis

Analyses were performed using STATA/MP 12.1 for Mac (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Demographic and clinical characteristics of the residents and the nurses are calculated as means with standard deviations (SD), and frequencies in case of categories.

The CMAI was not normally distributed, and therefore the questions of the CMAI were categorized in three types of agitation: physically non-aggressive agitation, physically aggressive agitation and verbal agitation.³⁶ Agitation was considered present if there was a score ≥ 3 on one or more items related to the specific type of agitation, which means the behaviour occurs at least once a week.^{9,37} The outcome (agitation measured with the CMAI) was then assessed with a logistic regression model. Since the aim of this study was explorative, each category of agitation was assessed in separate models with fixed effects for each independent variable concerning the characteristics of the nurses (age, working experience, gender and job characteristics).

Some nurses filled in the questionnaires of multiple residents and their scores cannot be considered independent. Therefore, a Huber-White sandwich estimator was used in the analyses to adjust for correlated responses within nurses.

Nurses did not always fill in the CMAI and the job characteristics questionnaires on the same day, because of that a variable was created reflecting the time difference between the completion of the CMAI and the completion of the job characteristics questionnaires. Also, a sensitivity analysis was performed without cases with a time difference of more than 30 days. For all tests, statistical significance was assumed at $p < 0.05$ in two-sided tests.

RESULTS

Resident characteristics

A total of 182 residents present from 22 dementia units were included in the analysis, their demographics are presented in Table 1. The cohort had a mean age of 83.9 years (SD 7.5), and 141 were women (77%). The mean GDS was 5.9 (SD 0.9). The mean CMAI score was 40.8 (SD 14.1), and 51.6% scored positive on physically nonaggressive agitated behaviour, 39.6% scored positive on aggressive behaviour and 36.3% scored positive on verbally agitated behaviour.

Nursing team characteristics

The CMAI scores of the residents were obtained by a total of 48 nurses. The nursing team members had a mean age of 34.7 years (SD 1.7), and 43 (89.6%) of them were women (1 missing data on gender). The mean working experience was 14.7 (SD 1.6) years.

Table 1. Demographics of the 182 nursing home residents with dementia

Age, mean (SD)	83.9 (7.5)
Female gender, N (%)	141 (77%)
GDS stages, N (%)	
Stage 3	0.9
Stage 4	6.3
Stage 5	23.2
Stage 6	46.4
Stage 7	23.2
Dementia type, N (%)	
Alzheimer's disease	76
Vascular dementia	30
Mixed dementia	20
Frontotemporal dementia	3
Dementia with Lewy bodies	3
Parkinson's disease	2
Dementia, not otherwise specified	34
Unknown	15
CMAI total score, mean (SD)	40.8 (14.1)

Abbreviations: CMAI, Cohen Mansfield Agitation Inventory; GDS, Global Deterioration Scale; SD, Standard Deviation.

Influence of nursing team characteristics on agitation

Table 2 shows the results for the association between the characteristics of the nurses and agitation measured with the CMAI. Social support measured with the 'Job Content Questionnaire' was significantly associated with physical aggression ($p=0.006$, OR 0.88 (95%CI 0.81 – 0.96)) with a higher score on nurses' perceived within-team social support being associated with a lower presence of physical aggression in residents. This finding remained significant when correcting for working experience, burnout symptoms and job satisfaction. The severity of cognitive impairment (GDS) was also significantly

associated with physical aggression measured with the CMAI ($p=0.049$, OR 1.67 (95%CI 1.01-2.79)), but did not correlate with social support (Spearman's $\rho=-0.025$, $p=0.79$) and was therefore not corrected for. All other nurse (job) characteristics were not significantly associated with physical aggression.

As shown in table 2, no nurse characteristics were significantly associated with non-aggressive physical agitation, though social support again showed a trend ($p=0.100$, OR 0.91 (95% CI 0.82-1.02)). None of the characteristics of the nursing team were associated with verbal agitation measured with the CMAI.

A sensitivity analysis was performed without observations with a time difference of more than 30 days between completion of the CMAI and completion of the job characteristics questionnaires, but this did not influence the results.

Table 2. Associations between nurse characteristics and agitation

Nurse characteristics	Physically aggressive agitation			Physically non-aggressive agitation			Verbal agitation		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.01	0.97-1.05	0.760	1.01	0.98-1.05	0.540	1.00	0.97-1.04	0.830
Working experience	0.99	0.95-1.03	0.505	0.99	0.96-1.03	0.630	1.00	0.97-1.05	0.820
Gender	1.56	0.65-3.75	0.315	1.26	0.40-4.00	0.694	0.81	0.29-2.29	0.697
Workload	1.01	0.94-1.08	0.870	1.02	0.95-1.10	0.569	1.04	0.96-1.13	0.312
Social support	0.88	0.81-0.96	0.006	0.91	0.82-1.02	0.100	1.00	0.91-1.09	0.970
Autonomy	0.97	0.90-1.05	0.500	0.97	0.88-1.06	0.454	0.99	0.93-1.06	0.849
Burnout	1.09	0.98-1.22	0.095	1.07	0.98-1.18	0.127	1.06	0.95-1.19	0.282
Job satisfaction	0.98	0.89-1.08	0.680	0.94	0.84-1.06	0.298	1.07	0.95-1.20	0.252

DISCUSSION

The aim of this study was to explore possible influences of the characteristics of the nursing team, especially job characteristics, on agitation in residents with dementia. The results show that higher scores of perceived social support within the nursing team are associated with lower odds of physical aggression measured with the CMAI. However, no significant associations were found for job demands, autonomy, burnout symptoms and job satisfaction.

The findings complement a line of work by others on the influence of job characteristics on other outcomes that all point to the importance of social support or team climate. For instance, Backhaus et al.³⁸ found that team climate measured with the 14-item version of the Team Climate Inventory (TCI)³⁹ was significantly associated with staff-reported quality of care, whereas other factors such as total direct care staffing and hierarchy culture were not. Also, a study by Zuniga et al.⁴⁰ found that teamwork and safety climate were most strongly related to quality of care. Social support, teamwork and team climate are mutually dependent concepts since they are all related to the

social cohesion on a unit.

The results of the present study are also in line with studies focussing on the influence of organisational factors and nursing staff characteristics on the treatment of neuropsychiatric symptoms. A recent study showed that less benzodiazepines were used in units where the nursing staff perceived more social support from their supervisor.⁴¹ The same study also found that more social support from co-workers was associated with less use of physical restraints. The authors expected a relationship with other job characteristics, such as job demands and decision authority, and the use of psychotropic drugs and physical restraints, but only associations with social support were found, which is comparable to the present study.

Social support is a complex concept and probably interacts with job control and job demands, as described in the Job Demands-Control-Support model.^{20,21} As hypothesized in the introduction social support from co-workers or supervisors may help to cope with a high workload²⁴ and increase resilience to cope with agitation. Conversely, a lack of social support may emphasize a feeling that the individual nurse stands alone in dealing with the situation. A possible explanation for our finding that only physically aggressive agitation but not verbal agitation was associated with social support could be that physical agitation might be more distressing for nursing staff, and therefore they benefit more from the positive effects of high social support in the context of physically aggressive agitation. Also, with physical agitation working together may be even more important. Assuming that agitation might evolve in situations where the resident does not understand what another person is doing with him/her, working together may prevent aggression, e.g. by one nurse comforting and distracting the resident while the other nurse provides the care. This may be reflected in one of the items of the social support scale: 'my supervisor succeeds in organizing people to work together'. Taken together, social support may influence the nursing staff's perception of problematic behaviour and agitation in particular, and may also influence the way nurses cope with agitation. Aside from the nurse's perception of the situation, social support within the nursing team may contribute to an 'atmosphere of ease' as described by Edvardsson et al.⁴², which is hypothesized to increase patient wellbeing and consequently may reduce the prevalence of NPS.

This points to a possible new lead for research on the bidirectional interaction between nursing staff and patients that may lead to both vicious and/or virtuous cycles, where the context of work and team may significantly influence the direction of the cycle. Indeed, some explorative research has been done on relationship-oriented management in nursing homes and interventions to increase nursing teamwork^{43–45}, all indicating that investing in teamwork and better staff relationships will lead to better outcomes for residents and nursing team.

This study has several limitations. First, no conclusions can be made about the direction of the association between social support and agitation in this cross-sectional study. It is hypothesized that more social support within the nursing team leads to less agitation, but it could also be that less agitation leads to less job demands, a higher sense of control and more social support (reverse causality). Unfortunately the longitudinal data in the current study did not provide enough power for an analysis. Second, other nursing team characteristics such as burnout symptoms and job satisfaction were not associated with the prevalence of agitation. While this might reflect a true non-association, it could also be due to a lack of power. The current study is an explorative study, and a larger study with a bigger sample might find more associations. Third, the CMAI is based on observations and perceptions of the nursing team; this could be different from the actual amount of agitation on a ward. Next, the nurse participants in the study gave permission to participate in the study, it could be that nurses with already a high amount of burnout symptoms were less likely to participate. This might have given an underestimation of our findings and might be another reason the other variables gave no significant results.

CONCLUSION

Higher perceived social support within the nursing team is associated with a lower prevalence of physical aggression. Interventions aimed at improving social support within nursing teams may lead to less physical aggression in residents or a better coping with aggression. However, larger longitudinal studies are needed to study the direction of this association.

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CHAPTER 7

GENERAL DISCUSSION

The aim of this thesis is to gain insight into the associations between the psychosocial context and neuropsychiatric symptoms (NPS) in the different stages of mild cognitive impairment (MCI) and dementia: from people with MCI living at home to people with dementia in a nursing home. In this general discussion chapter, a synopsis of the main findings is presented as well as a synthesis with literature and reflection on methodological and conceptual considerations. Figure 1 provides a visual guidance for the reader on the cohesion of the different chapters in this thesis.

The outline of the discussion is as follows:

- firstly, the relationship between NPS and cognitive disorders is covered;
- secondly, the association between the psychosocial context and NPS in MCI and dementia in persons living at home is discussed;
- thirdly, the psychosocial context of NPS in persons with dementia living in a nursing home is considered.

Each paragraph is followed by its clinical implications. The discussion ends with future directions and the overall conclusion.

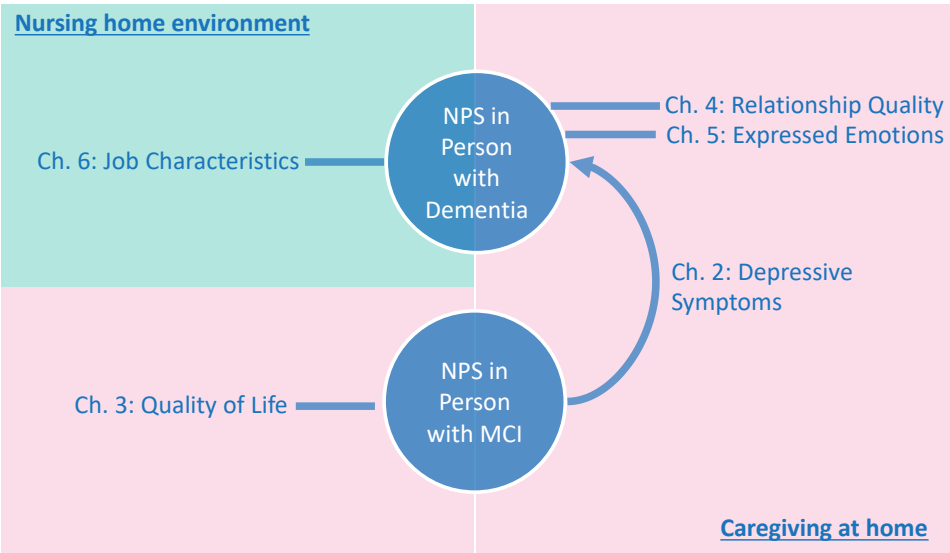


Figure 1. Context in which NPS are studied, including guidance in which chapters the specific associations are described.

RELATIONSHIP BETWEEN NPS AND COGNITIVE DISORDERS

NPS are an important phenomenon in MCI and dementia as they may cause negative outcomes in the person concerned, and also in the people around this person.¹⁻³ However, the nature of the association between NPS and cognitive disorders remains not fully understood. Depressive symptoms are considered a risk factor for dementia in the general population⁴; moreover, reviews suggest that NPS such as depressive symptoms are associated with the progression from MCI to dementia.^{5,6} In an attempt to contribute to a better understanding of the association between depressive symptoms, MCI and dementia a systematic review and meta-analysis of 35 studies was carried out (Chapter 2). The collected studies represent almost 15,000 persons with MCI from clinical settings and population studies. The systematic review concludes that depressive symptoms predict a higher dementia risk in community-dwelling persons with MCI. The pooled risk ratio shows that persons with depressive symptoms have a 1.69 times higher risk for dementia vs. persons with no depressive symptoms. Moreover, the result is consistent between studies as indicated by the very low between-study heterogeneity in risk ratio.

The direction of the relation between depressive symptoms, or other NPS, and conversion to dementia remains unclear. Multiple hypotheses are plausible: NPS as a psychological reaction to the arising cognitive difficulties, NPS as an independent risk factor or catalyzer for progression to dementia, NPS as an early sign of neurodegeneration due to reduced abilities to cope with stress, NPS as co-occurring with cognitive disorders due to shared etiological factors such as vascular risk factors, or as a consequence of the use of anticholinergic antidepressants.⁷⁻⁹

An often-studied hypothesis assumes that vascular risk factors are crucial in the association between depression and cognitive disorder: the vascular depression hypothesis.¹⁰ Unfortunately, in Chapter 2 we could not perform a statistical analysis focusing on mixed or vascular dementia because of insufficient data. The remaining hypotheses are also difficult to test, but it is likely that a combination of the above hypotheses contributes to the association, where the proportion of the specific contributions may differ from person to person.¹¹ For example, every person with dementia experiences the disease in a unique way, with various levels of stress¹² and various levels of stress-related behaviour. Some persons may experience a high level of stress due to experienced losses because of dementia, whilst others do not feel any stress. For those that experience a high level of stress, this might contribute to the emergence of NPS.¹³ The way a person copes with the stress, may also be influenced by the severity and the etiology of the neurodegenerative disease. Therefore, it is plausible that all hypotheses are true on a group level, yet for each individual the contribution of the factors is variable.

Conversely to the findings for community-dwelling persons with MCI, in clinical cohort studies heterogeneity was very high and no significant association between

depressive symptoms and progression to dementia was found (Chapter 2). Age seemed to partly explain the heterogeneity, and it should also be noted that age in the community-based studies was higher than in clinical studies (76.4 versus 71.8 resp.). In addition, in clinical cohort studies the amount of primarily depressed persons might be higher than in community-based studies. This assumption is in line with some clinical studies that found a negative association between depressive symptoms and conversion to dementia.^{14,15} Study characteristics other than setting did not explain any variability in outcome.

Clinical implications

The data of the meta-analysis described in Chapter 2 highlight the importance of screening for depressive symptoms in persons with MCI, at least for community-dwelling persons. Adequate treatment of these depressive symptoms might result in a better quality of life.^{16,17} It remains unclear whether treatment may also alter the progression to dementia, since the direction of the association, as mentioned above, is unclear. However, there is some evidence that treatment may even delay progression to dementia. One study in persons with MCI with previous depression showed a delayed progression to Alzheimer's disease after long-term SSRI treatment.¹⁸ On top of that, data from the same study indicate that persons with MCI and subsyndromal depressive symptoms receiving SSRI medication show less cognitive decline and less progression of atrophy of the grey matter than persons not receiving SSRI medication.¹⁹

THE PSYCHOSOCIAL CONTEXT OF NPS IN MCI AND DEMENTIA

Patient factors alone do not explain all variability in prevalence of NPS, and may be extended with the psychosocial context.²⁰ Therefore, the psychosocial context is also of interest in studying NPS in MCI or dementia. The relationship between NPS and the psychosocial environment is complex and the result of dynamic multidirectional interactions.^{21,22} An example from Chapter 5 in this thesis is that high levels of expressed emotions in the family caregiver are associated with higher levels of hyperactivity symptoms in the patient and an increased risk of institutionalization for the patient (Chapter 5).

In context of the above, biological, psychological and interpersonal factors may all play a role in NPS in MCI and dementia, and are dynamic in a sense that they can change over time but are relevant in all stages of cognitive decline. Therefore, we addressed different stages of the patient journey and caregiver career from persons with MCI and early stage dementia living at home to persons with severe stages of dementia living in a nursing home.²³ From the perspective that NPS in MCI and dementia are a disorder

or a health issue, the ‘dynamic biopsychosocial model of health’ is a particularly helpful framework to study the complex associations.^{24,25} Biological factors are for example age, severity of brain atrophy, cardiovascular disease or more specifically intracerebral small-vessel disease and medication. Psychological factors may consist of, among others, a psychiatric history or certain personality traits. Especially the interpersonal factors are complex and consist of multiple levels of interaction.²⁵ On the microlevel or ‘microsystem’, spouses, children, friends, neighbors or colleagues can all influence health by means of (a lack of) social support. For example, social isolation and feelings of loneliness have been associated with an increased risk of symptoms such as depression, anxiety and inactivity.²⁶ On top of that, professional caregivers such as nurses can play an important role in the interpersonal factors. Dementia care teams with care managers can lead to a better quality of life (QoL) and health outcomes in the person with dementia living at home.²⁷ In a nursing home setting the interaction between nurses and residents is crucial and person-centered care may result in less NPS.²⁸ On a macrolevel, the development of dementia friendly communities might result in more social inclusion and social support of the affected person and his or her loved ones.²⁹

Persons with MCI and dementia living at home

Continuing on the above, on a meso level, the psychological wellbeing of the family caregiver may influence the way he/she cares for the care receiver and therefore truly influence the health of the care receiver. These factors go back and forth, and one could say that the biopsychosocial factors of the person with dementia are connected with the biopsychosocial factors of the caregiver. NPS may lead to changes in the wellbeing and health-related quality of life of family caregivers. Indeed, in dementia, NPS are associated with a reduced QoL in the patient³⁰ as well as in the family caregiver³¹ (Chapter 3). However, in MCI we found no association between NPS and caregiver health-related QoL measured with the EQ5D-VAS³² in data from two Dutch multicenter studies (Chapter 3). The results indicated that family caregivers’ QoL was mainly associated with caregiver characteristics such as age, kind of relationship with the concerned person and possibly education. It is possible that no association with NPS was found, because of the average mild severity of the NPS in our study samples. Being a spouse was associated with a lower caregiver health-related QoL in Chapter 3, which is consistent with previous research.³³ In terms of the dynamic biopsychosocial model, this makes sense, as it seems logical that the biopsychosocial factors are more connected in the relationship between the person with dementia and his/ her spouse, than with a child or a neighbor, because of the more intensive contact.

The importance of this connection is further highlighted in Chapter 4, in which this connection is captured in the term relationship quality. A latent growth model was used to analyze relationship quality trajectories and potential determinants in persons with mild-to-moderate dementia and their caregivers in data from the European Actifcare

project.³⁴ NPS were associated with a decline in relationship quality measured with the Positive Affect Index³⁵ between caregivers and persons with mild-to-moderate dementia. Burden may be one of the mediating factors between NPS and relationship quality. NPS may lead to stress and burden in the caregiver³⁶, and this may affect the relationship quality. When the relationship quality declines, this may lead to a less empathic attitude towards the concerned person, to less communication and more irritability, this in turn may lead to more unmet needs.³⁷ Through these negative interaction sequences a rise in NPS may develop and health is affected. One of the ways to measure the interaction between the informal caregiver and a person with dementia is with the concept of expressed emotions (EE).³⁸ In the dynamic biopsychosocial model this can also be seen as a way to measure a part of the interpersonal factors. High levels of EE measured with the Five-Minute Speech Sample³⁹ in the family caregiver, especially high levels of critical comments, were indeed associated with hyperactivity symptoms in persons with dementia (Chapter 5). The difference was greater in caregivers scoring high on the subcategory critical comments. Moreover, during the 2-year follow-up, persons with dementia who had caregivers scoring high on critical comments were more likely to become admitted to a nursing home.

Clinical implications

Family caregivers have a crucial role in providing care for persons with dementia living at home. Since the number of persons with dementia is rising because of the aging population⁴⁰, the role of family caregivers will even be more essential. Health professionals and policy makers should be aware of the importance of the interactions between the psychosocial environment and persons with MCI or dementia living at home. In the case of Ms. V, from the vignette in the Introduction, her husband showed low levels of EE, the relationship quality remained good and no NPS arose. However, in other persons the opposite may be true: the co-occurrence of higher levels of EE, a declining relationship quality, a lower quality of life and the arising of NPS. It is therefore of great importance that informal caregivers feel supported and receive coaching when necessary.⁴¹ This could lead to lower levels of EE and a better relationship quality, which then could result in less NPS. Also, especially when direct contact is difficult, blended or E-health interventions could be feasible.⁴²

Residents with dementia in a nursing home

When a person with dementia gets admitted to a nursing home, the importance of the psychosocial context and the interpersonal factors may be even more important. The person with dementia, already struggling with (severe) cognitive and possibly emotional problems, leaves his or her familiar environment and has to adjust to a new context.⁴³ The physical appearance of the environment is important: the interior of the unit, the sound, temperature, sense of privacy, etc.^{44,45} Also, the size of the unit, type of care

and the number of visitors might be relevant.⁴⁶ Moreover, interpersonal factors in the dynamic biopsychosocial model can play a crucial role, such as the interaction with the nursing team.

The interaction between the nurses and the resident may be influenced by patient characteristics, but also by nurse characteristics. Nurse characteristics are aside from demographics such as age, education, working experience, also personality and the way the professional caregiver experiences his or her job. Job characteristics are for example job demands, job control and perceived social support within the nursing team as described in the Job Demands-Control-Support model.⁴⁷ A high workload and a low job satisfaction are for example associated with a higher prevalence of residents in nursing homes with violent behavior.⁴⁸ Chapter 6 focuses on a nursing home setting to investigate the association between job characteristics of the nursing team and the possible influence on agitation in residents with dementia. In 182 residents from 22 dementia care units a higher score of social support within the team was associated with a lower chance of physical aggression measured with the Cohen Mansfield Agitation Inventory (CMAI)⁴⁶ in residents with dementia. Social support consisted of support from coworkers and supervisors. The association was still significant after correcting for various factors such as burnout-symptoms and job satisfaction. No associations were found for other job characteristics such as job demands, autonomy, burnout symptoms and job satisfaction.

The concepts of 'social support within a nursing team', 'teamwork' and 'atmosphere' on a nursing home unit are related since they all describe the social cohesion on a unit. Just as social support, the team climate or the atmosphere in a nursing home unit seem important for outcomes, such as NPS, in residents with dementia. Several studies show that team climate is important for the quality of care.⁴⁹⁻⁵¹ It is likely that in the nursing home setting the associations are also multidirectional and dynamic. NPS, job characteristics, coping strategies of the individual nurses, staffing levels, resident factors, etc. will probably all interact in a complex network.

Clinical implications

In preventing and managing NPS, the psychosocial environment of the resident with dementia should not be overlooked. Naturally, also biological factors such as pain and psychological factors such as psychotrauma should be taken into account. However, our study shows that psychosocial factors, especially team characteristics in the nursing home unit are important to consider. In *Vignette Mr. B* in the Introduction of this Thesis there was a friendly atmosphere and a high amount of social support between nurses and probably this contributed to the low level of NPS. However, in other units there might be less social support, the atmosphere might be less friendly or a bit uneasy and this may result in higher levels of NPS. In an attempt to help the nursing team, doctors may prescribe psychoactive medication, resulting in side effects

and not solving the underlying problem.^{52,53} Interventions should preferably focus on enhancing interpersonal factors such as the teamwork and social support within the team. Multidisciplinary interventions such as the Grip on Challenging Behaviour care program (GRIP) have shown to influence the interactions between nurses and residents in a positive way and lead to less NPS and use of psychoactive drugs.⁵⁴

METHODOLOGICAL CONSIDERATIONS

The main strength of this thesis was the opportunity to study the association of the psychosocial context with NPS in cognitive disorders across different settings and through all stages of dementia. To be able to do this, datasets of multiple well-designed studies could be used or reused for the purposes of this thesis.

There are also some important methodological considerations. The reusing of data in Chapter 3 and Chapter 5 has the advantage of efficiency and consisted of relatively large populations. However, reusing data or secondary data analyses can present some challenges and risk for bias.^{55,56} For example, in Chapter 3 and 5 some interesting variables for the research questions were not measured and could therefore not be included in the analyses. These variables were addressed in the discussions of the concerning studies and could be included in future research.

In Chapter 3, 4, 5 and 6, NPS is measured by using instruments that are filled in by proxies (the informal or formal caregiver), such as the NPI and CMAI. As a consequence, this can be biased by the experienced burden of the caregiver that is known to influence the ratings of the severity of NPS.⁵⁷ However, from a caregiver perspective it is important to know the subjectively experienced NPS, because this represents the relevant burden. Moreover, alternative methods from a more objective perspective, such as observational instruments as Dementia Care Mapping (DCM), are often time-consuming and less evident to use in an individual home context.

Also, in Chapter 3, 4 and 5 the study sample is a memory clinic population, this results in a certain amount of sample selection bias. As we have seen in Chapter 2, the studied population (clinical or community-based) can have an important effect on the results. A memory clinic population could have a higher prevalence of NPS.⁵⁸ Moreover, certain informal caregivers will not participate with research because they feel more burdened or because they have less positive research attitudes.⁵⁹ This might have resulted in an underestimation of the associations, and the results of these studies might not be generalizable to a community-based population.

CONCLUSION AND FUTURE DIRECTIONS

The present thesis underlines the importance of taking the psychosocial context into account for a better understanding of neuropsychiatric symptoms in persons with cognitive disorders. This holds for the whole patient trajectory, i.e., from persons with mild cognitive impairments living at home to residents with dementia in a nursing home. To start, depressive symptoms may be important in the progression from mild cognitive impairment to dementia in community-dwelling persons. Future studies should further focus on the underlying mechanisms between neuropsychiatric symptoms and the development of dementia. Moreover, more research is needed to understand if treating neuropsychiatric symptoms in mild cognitive impairment may lead to a delayed progression to dementia.

The results of this thesis confirm the hypotheses that the relationship between neuropsychiatric symptoms in cognitive disorders and the psychosocial environment is a dynamic multidirectional interaction. In MCI, the quality of life of the informal caregiver is mainly influenced by caregiver characteristics. However, being a spouse is associated with a lower quality of life. In dementia, neuropsychiatric symptoms seem to influence caregiver quality of life. Moreover, neuropsychiatric symptoms are associated with a decline in relationship quality between a person with dementia and his or her informal caregiver, whereas more social support may be protective in maintaining a good relationship quality. Furthermore, high scores on caregiver expressed emotions, especially critical comments, are associated with more hyperactivity scores in persons with dementia. On top of that, higher scores on critical comments are associated with a higher risk of admission to a nursing home. Also, in the nursing home setting, more social support between nurses and supervisors may lead to less agitation in residents with dementia.

Future research is needed with a longitudinal design and preferably using objective ways to measure neuropsychiatric symptoms. This could lead to more insight into the network of the associations found between neuropsychiatric symptoms, the psychosocial context and dementia. Furthermore, expanding the use of methods such as LGM could help us gaining more insight in the complex interactions between the psychosocial context and neuropsychiatric symptoms in dementia, instead of looking at causal associations. This could lead to more tailored intervention programs.

Finally, in the education for dementia professionals more attention should be paid to the complex associations between the psychosocial context and neuropsychiatric symptoms in dementia. The importance of the well-being of the informal and formal caregivers in dementia should become an important focus.

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CHAPTER 8

SUMMARY

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SUMMARY

Dementia is characterized by the deterioration of cognitive functions, such as planning, memory, orientation and language. These symptoms interfere with the ability to perform everyday activities. The worldwide prevalence of dementia is rising and will expand to approximately 82 million in 2030, which has important consequences for health care systems. Mild cognitive impairment (MCI) can be seen as a transitional state between normal cognitive functioning and dementia. Persons with MCI neither have normal cognitive functioning nor dementia and have a preserved ability to perform everyday activities; not all persons with MCI will eventually develop dementia. In dementia as well as in MCI neuropsychiatric symptoms (NPS) often arise. NPS are for example symptoms such as depression, anxiety, apathy, psychosis and sleep disturbances. NPS are associated with negative health effects in the person with a cognitive disorder, but also in the family caregiver, and increase the risk for nursing home admission. NPS are partly associated with patient-related factors, but also with the physical and psychosocial environment. Therefore, the aim of this thesis was to study the relationship between the psychosocial context and neuropsychiatric symptoms in the different stages of MCI and dementia.

In **Chapter 2**, the possible impact of depressive symptoms, as a neuropsychiatric symptom, on the progression from MCI to dementia was studied. In this systematic review and meta-analysis 35 studies were included, representing almost 15,000 persons with MCI from both clinical settings and population studies. Meta-regression analyses were done to examine study characteristics as possible sources of variability in study outcomes. Results showed that in community-dwelling persons depressive symptoms predict a higher dementia risk. In clinical cohort studies heterogeneity was very high and no significant association between depressive symptoms and progression to dementia was found. Study characteristics other than setting did not explain any variability in outcome. Several hypotheses can be postulated concerning the direction of the association in the community-dwelling persons, one of this hypotheses is the vascular depression hypothesis.

Chapter 3 describes a study analyzing the health-related quality of life in family caregivers in MCI and its possible determinants such as NPS. Also, a comparison with mild dementia is made. The quality of life of the caregiver was measured with the EQ5D-VAS, which is a health-related quality of life instrument. The mean EQ5D-VAS in caregivers of persons with MCI did not differ from that of caregivers in mild dementia and was relatively high compared to standardized scores. Bivariate and multiple regression analyses indicated that especially caregiver characteristics seem to influence caregiver quality of life in MCI, and not patient characteristics such as global cognitive functioning or NPS. Being a spouse, compared to being a child/ or other caregiver, and being older was associated with a lower EQ5D-VAS. In a subgroup of family caregivers, who identified themselves as persons actually providing care, there were indications that problems with own mental and/or physical health as well

as problems combining care tasks with daily activities are associated with lower EQ5D-VAS scores.

Also important for quality of life in dementia, may be relationship quality of the person with dementia and his or her family caregiver. Therefore, in **Chapter 4** a latent growth model was used to analyze relationship quality trajectories and potential determinants in persons with mild-to-moderate dementia and their informal caregivers in data from the European Actifcare Project. In the caregiver group, relationship quality measured with the Positive Affect Index declined during the one-year follow-up period. The Positive Affect Index is a 5-item scale to assess current perceived relationship quality addressing closeness, communication quality, similar views of life, engaging in shared activities and getting along in general. Relationship quality scored by persons with dementia did not change during follow-up. Caregiver sense of coherence and being a spouse was associated with better relationship quality scored by the caregiver on baseline. More social support seemed to be a possible protector in maintaining a good relationship quality scored by the caregiver. Neuropsychiatric symptoms were related to a decline in relationship quality in caregivers during the follow-up period.

In **Chapter 5**, the aim of the study was to examine possible associations between expressed emotions in informal caregivers and persons with dementia living at home. Expressed emotions (EE) is a concept, developed in schizophrenia studies, that captures interpersonal interactions. In dementia, it can measure how much criticism, hostility, or emotional overinvolvement the family caregiver expresses when speaking about a relative with dementia. In Chapter 5, EE was measured with the Five-Minute Speech Sample in 112 informal caregivers of persons with dementia. High levels of EE were associated with hyperactivity symptoms in persons with dementia at baseline and some other time points during the two-year follow-up period. The difference was greater in caregivers scoring high on the subcategory critical comments. In this group the risk of admission to a nursing home was also increased during follow-up. The association between EE and NPS is likely to be bidirectional.

Chapter 6 focused on a nursing home setting to investigate the association between nurses' job characteristics and the prevalence and severity of NPS, specifically agitation, in residents with dementia. Job characteristics are for example job demands, control, and social support, as described in Karasek's Job Demands-Control-Support model. In 182 residents from 22 dementia care units a higher score of social support within the team was associated with a lower chance of physical aggression measured with the Cohen Mansfield Agitation Inventory (CMAI) in residents with dementia. Social support consisted of support from coworkers and supervisors. The association was still significant after correcting for various factors such as burnout-symptoms and job satisfaction. No associations were found for other job characteristics such as job demands, autonomy, burnout symptoms and job satisfaction.

In **Chapter 7**, the general discussion of this thesis, a synopsis of the main results

of this thesis is presented, a synthesis with relevant literature is given and clinical implications are discussed.

SAMENVATTING

Dementie wordt gekenmerkt door de achteruitgang van cognitieve functies, zoals planning, geheugen, oriëntatie en taal. Deze symptomen interfereren met het vermogen om dagelijkse activiteiten uit te voeren. De wereldwijde prevalentie van dementie stijgt en zal groeien tot ongeveer 82 miljoen in 2030, wat belangrijke gevolgen heeft voor de gezondheidszorg. Milde cognitieve stoornissen (MCI) kunnen worden gezien als een overgangstoestand tussen normaal cognitief functioneren en dementie. Personen met MCI hebben cognitieve problemen maar geen dementie en hebben hun vermogen om dagelijkse activiteiten uit te voeren behouden; niet alle personen met MCI zullen uiteindelijk dementie krijgen. Zowel bij dementie als bij MCI treden vaak neuropsychiatrische symptomen (NPS) op. NPS zijn bijvoorbeeld depressie, angst, apathie, psychose en slaapproblemen. NPS gaan gepaard met negatieve gezondheidseffecten bij de persoon met een cognitieve stoornis, maar ook bij de mantelzorger, en verhogen het risico op verpleeghuisopname. NPS hangen deels samen met patiëntgebonden factoren, maar ook met de fysieke en psychosociale omgeving. Het doel van dit proefschrift was om de relatie tussen de psychosociale context en neuropsychiatrische symptomen in de verschillende stadia van MCI en dementie te bestuderen.

In **Hoofdstuk 2** is de mogelijke impact van depressieve symptomen, als een neuropsychiatrisch symptoom, op de progressie van MCI naar dementie bestudeerd. In deze systematische review en meta-analyse zijn 35 studies opgenomen, die bijna 15.000 personen met MCI vertegenwoordigen uit zowel klinische settings als populatiestudies. Meta-regressieanalyses zijn uitgevoerd om studiekenmerken te onderzoeken als mogelijke bronnen van variabiliteit in studieresultaten. De resultaten tonen aan dat depressieve symptomen bij thuiswonende personen een hoger risico op dementie voorspellen. In klinische cohortstudies is de heterogeniteit zeer hoog en is geen significant verband gevonden tussen depressieve symptomen en progressie naar dementie. Andere studiekenmerken dan de setting verklaarden geen significante variabiliteit in uitkomst. Er kunnen verschillende hypothesen worden gepostuleerd met betrekking tot de richting van de associatie bij thuiswonende personen, een van deze hypothesen is de vasculaire depressiehypothese.

Hoofdstuk 3 beschrijft een studie die de gezondheidsgerelateerde kwaliteit van leven van mantelzorgers in MCI en de mogelijke determinanten daarvan, zoals NPS, analyseert. Ook wordt een vergelijking gemaakt met milde dementie. De kwaliteit van leven van de mantelzorger werd gemeten met de EQ5D-VAS, een instrument voor de gezondheidsgerelateerde kwaliteit van leven. De gemiddelde EQ5D-VAS bij mantelzorgers van personen met MCI verschilt niet van die van mantelzorgers bij milde dementie en is relatief hoog in vergelijking met gestandaardiseerde scores. Bivariate en multiële regressieanalyses geven aan dat vooral kenmerken van de mantelzorger de kwaliteit van leven van de mantelzorger lijken te beïnvloeden in MCI, en niet patiëntkenmerken zoals globaal cognitief functioneren of NPS. Echtgeno(o)t(e) zijn, is geassocieerd met een lagere EQ5D-VAS vergeleken met het zijn van een kind/of andere verzorger, ook

het hebben van een oudere leeftijd is geassocieerd met een lagere EQ5D-VAS. In een subgroep van mantelzorgers, die zich identificeerden als personen die daadwerkelijk zorg verlenen, zijn er aanwijzingen dat problemen met de eigen mentale en/of fysieke gezondheid en problemen met het combineren van zorgtaken met dagelijkse activiteiten geassocieerd zijn met lagere EQ5D-VAS-scores.

Voor het welzijn van een persoon met dementie is ook de kwaliteit van de relatie tussen de persoon met dementie en zijn of haar mantelzorger belangrijk. Daarom is in **Hoofdstuk 4** een 'latent grow model' gebruikt om het beloop van de kwaliteit van de relatie en potentiële determinanten te analyseren bij personen met milde tot matige dementie en hun mantelzorgers middels gegevens van het Europese Actifcare Project. De door mantelzorgers beleefde kwaliteit van de relatie, gemeten met de Positive Affect Index, nam af gedurende de follow-up periode van een jaar. De Positive Affect Index is een schaal met 5 items om de huidige waargenomen relatiekwaliteit te beoordelen, met betrekking tot nabijheid, communicatiekwaliteit, vergelijkbare levensbeschouwingen, deelname aan gedeelde activiteiten en in het algemeen met elkaar op kunnen schieten. De kwaliteit van de relatie gescoord door personen met dementie veranderde niet tijdens follow-up. De mantelzorger zijn of haar gevoel van samenhang ('sense of coherence') en het zijn van partner/echtgenoot/echtgenote is geassocieerd met een betere relatiekwaliteit gescoord door de mantelzorger op baseline. Het hebben van 'meer sociale steun' lijkt een mogelijke beschermer te zijn bij het in stand houden van een door de mantelzorger gescoorde goede relatiekwaliteit. NPS zijn gerelateerd aan een afname van de relatiekwaliteit gescoord door mantelzorgers tijdens de follow-up periode.

In **Hoofdstuk 5** is het doel van de studie om mogelijke associaties te onderzoeken tussen geuite emoties bij mantelzorgers en NPS van thuiswonende personen met dementie. Expressed emotions (EE) is een concept, ontwikkeld in schizofrenie-studies, dat interpersoonlijke interacties vastlegt. Bij dementie kan het meten hoeveel kritiek, vijandigheid of emotionele overbetrokkenheid de mantelzorger uit wanneer hij spreekt over een familielid met dementie. In hoofdstuk 5, is EE gemeten met de Five-Minute Speech Sample bij 112 mantelzorgers van personen met dementie. Hoge niveaus van EE zijn geassocieerd met hyperactiviteitsymptomen bij personen met dementie bij aanvang en op enkele volgende tijdstippen tijdens de follow-up periode van twee jaar. Het verschil is groter bij mantelzorgverleners die hoog scoorden op de subcategorie kritische opmerkingen. Bij deze groep is het risico op opname van de persoon met dementie in een verpleeghuis ook verhoogd tijdens de follow-up. De associatie tussen EE en NPS is waarschijnlijk bi-directioneel.

Hoofdstuk 6 richt zich op een verpleeghuissetting om het verband te onderzoeken tussen de werk-gerelateerde kenmerken van verpleegkundigen en de prevalentie en ernst van NPS, in het bijzonder agitatie, bij bewoners met dementie. Werk-gerelateerde kenmerken zijn bijvoorbeeld de ervaren werkeisen, de ervaren controle over het werk

en sociale steun, zoals beschreven in het Job Demands-Control-Support-model van Karasek. Er zijn 182 bewoners van 22 verpleegafdelingen voor personen met dementie en een deel van hun verpleegkundige teams meegenomen in het onderzoek. Fysieke agressie is gemeten met de Cohen Mansfield Agitation Inventory (CMAI). In de studie is een hogere score op sociale steun binnen het team geassocieerd met een lagere kans op fysieke agressie. Sociale steun bestaat uit steun van collega's en leidinggevenden. De associatie is nog steeds significant na correctie voor verschillende factoren zoals burn-out-symptomen en werktevredenheid. Er zijn geen associaties gevonden voor andere functietekenen zoals werkeisen, autonomie, burn-outsymptomen en werktevredenheid.

In **Hoofdstuk 7**, de algemene discussie van dit proefschrift, wordt een samenvatting van de belangrijkste resultaten van dit proefschrift gepresenteerd, een synthese met relevante literatuur gegeven en klinische implicaties besproken.

APPENDIX

IMPACT PARAGRAPH

DANKWOORD

ABOUT THE AUTHOR

LIST OF PUBLICATIONS

IMPACT PARAGRAPH

The impact paragraph describes the scientific and societal impact of the results presented in this thesis. In addition, target groups are identified for whom the findings are relevant. Moreover, it is pointed out how these specific target groups can be reached and informed about the research findings.

Aim and key findings

Dementia has a huge impact on affected persons, their family and society. The worldwide prevalence will expand to approximately 82 million in 2030¹ and this has important consequences for health care. Neuropsychiatric symptoms (NPS) – as covered in this thesis - play a role in the aforementioned upcoming increase of numbers of people with dementia, as they can cause various negative outcomes for the patient. NPS are behavioral changes that commonly develop during the different stages of dementia and include for example anxiety, depressive symptoms, psychosis and sleep disturbances. NPS are associated with patient-related factors, but also with the physical and psychosocial environment.² NPS can also lead to negative health effects in the informal caregiver³ and are an important risk factor for transferring from living at home to a nursing home admission. Considering the high dementia prevalence, the role of informal caregivers will only increase and the pressure on nursing homes will grow. In light of the above, the aim of this thesis was to gain more insight into the relationship between the psychosocial context and neuropsychiatric symptoms in the different stages of mild cognitive impairment (MCI) and dementia.

The first study of this thesis focused on the association between depressive symptoms and the progression from MCI to dementia. A systematic review and meta-analysis of the existing literature (Chapter 2) showed that depressive symptoms are associated with an increased risk in the progression from MCI to dementia in community-dwelling persons, but not in clinical populations. The other studies in this thesis focused on the understanding of the relationship between neuropsychiatric symptoms in cognitive disorders and the psychosocial environment. In MCI, the quality of life of the informal caregiver and its potential determinants, including caregiver and person with MCI characteristics such as NPS, were studied (Chapter 3). In this study being a spouse was associated with a lower caregiver quality of life. In addition, the quality of life of the informal caregiver was mainly influenced by caregiver characteristics. However, in dementia, NPS influence the quality of life of the informal caregiver. In line with this, in the following study NPS were associated with a decrease in relationship quality between a person with dementia and his or her informal caregiver over a year (Chapter 4). In the same study social support was associated with maintaining a good relationship. In another study the concept of *expressed emotions* was used to capture the interaction between the caregiver and the person with dementia (Chapter 5). High scores on caregiver expressed emotions, especially critical comments, were associated with more hyperactivity scores in persons with dementia. In addition, critical comments were also

associated with more nursing home admissions. In the last study in this thesis, in a nursing home setting, the results showed that more social support between nurses and supervisors may lead to less agitation in residents with dementia (Chapter 6). Altogether, the results of this thesis confirm the hypothesis that NPS in cognitive disorders and the psychosocial environment interact in a dynamic multidirectional way.

Scientific relevance

This thesis provides more insights into the complex association between the psychosocial environment and NPS in MCI and dementia. The systematic review and meta-analysis (Chapter 2) contribute to the knowledge about the relationship between depressive symptoms and cognitive disorders, specifically the progression from MCI to dementia. The fact that depressive symptoms increased the risk for progression to dementia is not only important because of its consequences for the prognosis of the person with MCI, but also for researchers, as they want to better identify which people with MCI have higher risks of eventually getting dementia, and which will not. This might also lead to more starting points for setting up intervention studies.

In Chapter 3, 4 and 5 different measurements were used to analyze interactions between the psychosocial environment and NPS in cognitive disorders in persons living at home. We used concepts as caregiver quality of life and relationship quality. Also, we used expressed emotions to measure the interaction between the informal caregiver and person with dementia. The results showed that the association is complex and consists of dynamic multidirectional interactions. It is important that in future research these interactions will be further unraveled to come to a more complete understanding. The measurements used in this thesis were feasible, and the studies demonstrate that these measurements are important to take into account in dementia research.

In a nursing home setting, the influence of job characteristics of the nursing team on agitation in residents with dementia was explored (Chapter 6). These job characteristics are described in Karasek's Job Demands-Control-Support model^{4,5}, which is a relevant framework to take into account when studying the psychosocial context in a nursing home setting. Our explorative study showed the importance of social support and researchers can use this study as a stepping stone for a larger longitudinal study on social support within nursing teams.

Societal relevance

As described above, NPS have a huge impact on quality of life of the affected person and result in higher levels of burden for the caregiver. NPS are a major reason for nursing home admission and for the prescription of psychoactive drugs. Lowering the prevalence of NPS could delay or prevent nursing home admission and result in a better quality of life. This thesis confirms the importance of the psychosocial environment in dementia and the complex interaction with NPS. Policy makers in health care should

therefore focus on the psychosocial environment by giving attention to both informal and formal caregivers. Social support for informal caregivers, but also social support within a nursing team could make it easier to cope with challenging behavior. Moreover, paying attention to the interactions between a person with dementia and a caregiver, for example by means of expressed emotions, could result in less hyperactive behavior.

In dementia, NPS seem to influence caregivers' quality of life, this highlights the importance of the interaction between the psychosocial environment and NPS. The finding that relationship quality declines in dementia, and that this is mediated by NPS and (a lack of) social support might be a lead for more targeted interventions. However, the finding that the quality of life of the informal caregiver in MCI and mild dementia is relatively good, and mainly depends on caregiver characteristics is principally a positive and encouraging finding. While MCI and mild dementia can place a burden on a caregiver, it does in the same time not affect caregiver's reported quality of life in general. It is important that also these positive outcomes are communicated to the persons concerned, as they may have a supporting and encouraging effect.

The thesis is also relevant for educational purposes to build more awareness about the importance of the psychosocial environment in dementia and the possible relationship with NPS. Health care professionals such as case managers, nurses and doctors can be made more aware that for reducing NPS, instead of looking primarily at psychoactive drugs, one should also pay more attention to the people around a person with MCI or dementia. Finally, students should be made aware that coaching and supporting caregivers not only may result in better outcomes for the persons with MCI or dementia, but also for the caregivers themselves.

Target groups

The results of this thesis are relevant for various groups. Firstly, the findings are relevant for researchers in the field of dementia as the different studies in this thesis give suggestions for further research. Secondly, policy makers could use the results of this and other research as a reason to improve the support and coaching of informal caregivers. Also, policy makers should take notice of the importance of the wellbeing of nursing teams, as this will result in better job satisfaction, but probably also in better patient outcomes. Thirdly, the results of this thesis are important for health care professionals such as nurses, doctors and psychologists. They can be made more aware that the health and wellbeing of persons with MCI and dementia is not only affected by the disease itself, but results from a complex interaction with dynamic psychological and social factors. Lastly, but certainly not least, the results are relevant for persons with dementia and caregiver groups. Raising awareness for the importance of the interaction between the psychosocial environment and NPS is beneficial for these groups since this could lead to more understanding and new developments.

Activity

The target groups of the results of this thesis are informed in several ways. Four of the studies in this thesis are already published in international medical journals, and one of the studies is submitted for publication in an international medical journal. Some of the published studies already have been cited multiple times. Furthermore, the results of this thesis will be presented at multiple regional conferences for clinicians. Lastly, in education I fulfill a personal role as a trainer of old-age psychiatry and clinical geriatrics residents, where I make sure that sufficient attention is paid to the importance of the psychosocial context in patients with cognitive disorders.

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DANKWOORD

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ABOUT THE AUTHOR

Eva Tan was born on March 25th in Nijmegen, the Netherlands. She grew up in Deurne and finished her VWO at the Willibrord Gymnasium. She started her medicine study in 2002 at the Maastricht University and graduated in 2008. During her medicine study she developed a growing interest in psychiatry, first in child psychiatry and later in old-age psychiatry. From 2009 to 2013 she was a resident in psychiatry at the 'Universitaire opleiding psychiatrie te Zuid-Limburg'. During her residency her interest in scientific research grew, especially about neuropsychiatric symptoms in cognitive disorders. After finishing her residency, she worked as an old-age psychiatrist at the Institute for Mental Health Care, GGzE, Eindhoven, and at Reinier van Arkel, Den Bosch. In addition to her clinical work as a psychiatrist, she also started her PhD trajectory. Currently she works as an old-age psychiatrist at a neuropsychiatry ward at the GGzE, Eindhoven. She is also active in geriatric psychiatry training and education.

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