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The interaction of caregiver expressed emotions and neuropsychiatric symptoms in persons with dementia: a longitudinal cohort study

Eva Y.L. Tan1,2, Marjolein E. de Vugt1, Kay Deckers1, Jos M.G.A. Schols1,3, Frans R. J. Verhey1

1Alzheimer Centre Limburg, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, the Netherlands
2Reinier van Arkel Mental Health Institute, ’s-Hertogenbosch, the Netherlands
3Department of Family Medicine and Department of Health Services Research, Caphri, Maastricht, the Netherlands

Correspondence to: Eva Tan; eva.tan@maastrichtuniversity.nl

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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.
Strengths and limitations of this study

- This is a longitudinal cohort study with a relatively large sample size with 2-year follow-up.

- The association between expressed emotions in caregivers and neuropsychiatric symptoms in persons with dementia living at home was examined taking into account multiple confounding factors.

- Factors associated with expressed emotions were explored as well as the association between expressed emotions and institutionalization rate.

- We used the Five-Minute Speech Sample to measure expressed emotions; this is a feasible instrument, but not the gold standard for measuring the level of expressed emotions.

- The level of expressed emotions was only assessed at baseline, therefore we were not able to study possible changes in expressed emotions over time.
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]. It was then used in various other studies concerning, for example, bipolar disease and eating disorders. 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 caregivers taking care of PwD [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]. A recent study in Hong Kong showed that the negative impact of NPS on outcomes in dementia caregivers was mediated by EE [13]. 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 it is a bit of both: some caregivers will always show a higher EE compared to others, but the level of EE can change over time [9] and might therefore be modifiable. A recent study in caregivers of patients with Alzheimer’s disease found that depressive temperament traits might predict higher levels of 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 EE [15], and they suggest that educating these daughters may help reduce stress.

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 study [16] were used to (1) examine a possible association between 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 focusing on the course and risk factors of NPS in dementia [16]. 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 dementia [17], 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) [18]. Patient dependency with regard to daily activities was measured with the Interview for Deterioration in Daily living activities in Dementia (IDDD) [19]. Furthermore, the severity of dementia was measured with the Global Deterioration Scale (GDS) [20].

NPS were measured with the Neuropsychiatric Inventory (NPI) [21]. 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 [22]. 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) [23]. 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. [23]. 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 fulfill 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) [21]. Caregiver subjective competence was measured with the Short Sense of Competence Questionnaire (SSCQ) [24]. 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) [25].

Personality traits were assessed with the NEO-Five Factor Inventory (NEO-FFI) [26]. The NEO Five-Factor Inventory (NEO-FFI) is a shortened version of the NEO Personality Inventory-Revised [26].

**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 χ² 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.

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). 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, or total NPI scores; 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 the PwD had a slightly higher mean GDS score (4.3 vs. 4.0, p=0.022).

The mean age of the caregivers was 63.8 years (SD = 12.2, range 36-90), 77 (64.7%) were women, 64 (53.5%) were spouses, 47 (39.5%) were children, and 8 (7.2%) had another relationship (e.g., close friends). The mean duration of care was 27.3 months (SD = 25.6, range 3-120), and the caregivers spent a mean of 94.8 contact hours per week (SD = 70.3, range 3 - 168) with the PwD.

The PwD had a mean age of 78.5 (SD = 8.4, range 56-99), and 70 (58.8%) were women. Ninety PwD (75.6%) had Alzheimer's disease, 20 (16.8%) vascular dementia, 2 (1.7%) fronto-temporal dementia, 3 (2.5%) Parkinson's disease, 1 primary progressive dementia and 3 (2.5%) mixed dementia. The mean duration of illness was 42.9 months (SD = 31.0, range 6 - 120), and the mean MMSE score was 18.3 (SD = 4.7). The mean GDS score was 4.1, with 18.5% having stage 3 cognitive functioning, 53.8% stage 4, 26.9% stage 5 and 0.8% stage 6.

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 | High-EE | P-value |
|---------------|--------|---------|---------|
| N             | 76     | 36      |         |

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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   |

EE, expressed emotion. GDS, Global deterioration scale. MMSE, Mini Mental State Examination

Expressed emotion as predictor of neuropsychiatric symptoms at baseline

There was no difference between the EE groups in mean baseline NPI score (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).

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.

**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)).

**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.

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.   | 9.6 vs. 14.6 | 11.7 vs. 16.1 | 11.8 vs. 16.2 | 10.5 vs. 17.4 | 11.1 vs. 12.7 |
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 [12,13,27]. It seems most likely that this direction is at least bidirectional, as also described previously by Hooley et al.[8] 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-Mansfield [28], 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. 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 caregivers [29] and was found to be associated with deterioration of the relationship quality in a previous study using MAASBED [30], but we did not find an association between apathy and high EE in the present study.

| Low vs. High | p = 0.002 | p = 0.011 | p = 0.008 | p = 0.009 | p = 0.437 |
|--------------|-----------|-----------|-----------|-----------|-----------|
| p = 0.015    | p = 0.084 | p = 0.079 | p = 0.071 | p = 0.71  |

Critical comments: 9.6 vs. 16.1
11.4 vs. 18.6
11.5 vs. 19.4
10.4 vs. 22.2
10.3 vs. 14.7

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.
favours the hypothesis that high EE is not purely elicited by the emotional burden related to neuropsychiatric symptoms, such as hyperactivity.

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 [31]. 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 [32,33]. 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 [34]. 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 [35]. 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 [36], 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) [36]. Additionally, the level of EE was only assessed at baseline, so we could not study possible changes in EE over time. 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. 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.

Contributors – EYLT: researched and analysed the data, wrote the manuscript. MEV: reviewed/edited the manuscript, contributed to the discussion. KD: researched and analysed the data, reviewed/edited the manuscript. JMAGS: reviewed/edited the manuscript, contributed to the discussion. FRJV: reviewed/edited the manuscript, contributed to the discussion.

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

![Graph showing mean hyperactivity score on the NPI by EE-group with low expressed emotions and high expressed emotions depicted](image1.png)

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

![Graph showing mean hyperactivity score on the NPI by EE subgroups critical vs. non-critical](image2.png)
| Section/Topic          | Item # | Recommendation                                                                 | Reported on page # |
|-----------------------|--------|---------------------------------------------------------------------------------|--------------------|
| **Title and abstract**| 1      | *(a)* Indicate the study’s design with a commonly used term in the title or the abstract  | 1                  |
|                       |        | *(b)* Provide in the abstract an informative and balanced summary of what was done and what was found | 2                  |
| **Introduction**      |        |                                                                                   |                    |
| Background/rationale   | 2      | Explain the scientific background and rationale for the investigation being reported | 4,5                |
| Objectives            | 3      | State specific objectives, including any pre-specified hypotheses               | 5                  |
| **Methods**           |        |                                                                                   |                    |
| Study design          | 4      | Present key elements of study design early in the paper                          | 5                  |
| Setting               | 5      | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5                  |
| Participants          | 6      | *(a) Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  | 5                  |
|                       |        | *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  |
|                       |        | *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants  |
|                       |        | *(b) Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed cases  |
|                       |        | *Case-control study*—For matched studies, give matching criteria and the number of controls per case  |
| Variables             | 7      | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5,6,7              |
| Data sources/ measurement | 8*     | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 5,6,7              |
| Bias                  | 9      | Describe any efforts to address potential sources of bias                         | 6                  |
| Study size            | 10     | Explain how the study size was arrived at                                         | 8                  |
| Quantitative variables | 11     | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods   | 12     | *(a) Describe all statistical methods, including those used to control for confounding  | 7                  |
|                       |        | *(b) Describe any methods used to examine subgroups and interactions                | 7                  |
|                       |        | *(c) Explain how missing data were addressed                                       |                    |
|                       |        | *(d) Cohort study*—If applicable, explain how loss to follow-up was addressed       |                    |
|                       |        | *Case-control study*—If applicable, explain how matching of cases and controls was addressed |
| Results | Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy |
|---------|--------------------------------------------------------------------------------------------------|
|         | (e) Describe any sensitivity analyses                                                            |
|         |                                                                                                  |
|         | **Participants**                                                                                 |
|         | 13*                                                                                             |
|         | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
|         | 8                                                                                               |
|         | (b) Give reasons for non-participation at each stage                                             |
|         | 8                                                                                               |
|         | (c) Consider use of a flow diagram                                                               |
|         |                                                                                                  |
|         | **Descriptive data**                                                                            |
|         | 14*                                                                                             |
|         | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
|         | 8,9                                                                                             |
|         | (b) Indicate number of participants with missing data for each variable of interest               |
|         |                                                                                                  |
|         | **Outcome data**                                                                                |
|         | 15*                                                                                             |
|         | (a) **Cohort study**—Report numbers of outcome events or summary measures over time               |
|         | 8,9,10,11                                                                                       |
|         | (b) **Case-control study**—Report numbers in each exposure category, or summary measures of exposure|
|         |                                                                                                  |
|         | (c) **Cross-sectional study**—Report numbers of outcome events or summary measures                |
|         |                                                                                                  |
|         | **Main results**                                                                                |
|         | 16                                                                                              |
|         | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
|         | 8,9,10,11                                                                                       |
|         | (b) Report category boundaries when continuous variables were categorized                        |
|         |                                                                                                  |
|         | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
|         |                                                                                                  |
|         | **Other analyses**                                                                              |
|         | 17                                                                                              |
|         | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses       |
|         | 10,11                                                                                           |
|         |                                                                                                  |
|         | **Discussion**                                                                                  |
|         | 18                                                                                              |
|         | Summarise key results with reference to study objectives                                          |
|         | 11                                                                                              |
|         | **Limitations**                                                                                 |
|         | 19                                                                                              |
|         | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
|         | 12                                                                                              |
|         | **Interpretation**                                                                              |
|         | 20                                                                                              |
|         | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
|         | 11, 12                                                                                          |
|         | **Generalisability**                                                                           |
|         | 21                                                                                              |
|         | Discuss the generalisability (external validity) of the study results                            |
|         | 11, 12                                                                                          |
|         | **Other information**                                                                          |
|         | 22                                                                                              |
|         | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |
|         | 13                                                                                              |

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

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

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The interaction of caregiver expressed emotions and neuropsychiatric symptoms in persons with dementia: a longitudinal cohort study

Eva Y.L. Tan¹², Marjolein E. de Vugt¹, Kay Decker¹, Jos M.G.A. Schols¹³, Frans R. J. Verhey¹

¹Alzheimer Centre Limburg, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, the Netherlands

²Reinier van Arkel Mental Health Institute, ’s-Hertogenbosch, the Netherlands

³Department of Family Medicine and Department of Health Services Research, Caphri, Maastricht, the Netherlands

Correspondence to: Eva Tan; eva.tan@maastrichtuniversity.nl

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Figures: 2
Tables: 3
Supplementary figures: 1
Supplementary tables: 2
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.
Strengths and limitations of this study

- This is a longitudinal cohort study with a relatively large sample size with 2-year follow-up.
- The association between expressed emotions in caregivers and neuropsychiatric symptoms in persons with dementia living at home was examined taking into account multiple confounding factors.
- Factors associated with expressed emotions were explored as well as the association between expressed emotions and institutionalization rate.
- We used the Five-Minute Speech Sample to measure expressed emotions; this is a feasible instrument, but not the gold standard for measuring the level of expressed emotions.
- The level of expressed emotions was only assessed at baseline, therefore we were not able to study possible changes in expressed emotions over time.
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 Lawton [13] 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 EE [15], 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 time [9] 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 study [17] 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 dementia [18], 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 χ² 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 | High-EE | P-value |
|----------------------|--------|---------|---------|
|                      | N = 76 | N = 36  |         |
| 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   |

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

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

|                      | Low-EE | High-EE | P-value |
|----------------------|--------|---------|---------|
|                      | N = 76 | N = 36  |         |
| 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

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 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).

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.

**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 did not have a major impact on the results.

**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 | 11.7 vs. 16.1 | 11.8 vs. 16.2 | 10.5 vs. 17.4 | 11.1 vs. 12.7 |
|                | p = 0.015    | p = 0.084 | p = 0.079 | p = 0.071 | p = 0.71 |
| Critical comments: |          |          |          |          |          |
| low vs. high   | 9.6 vs. 16.1 | 11.4 vs. 18.6 | 11.5 vs. 19.4 | 10.4 vs. 22.2 | 10.3 vs. 14.7 |
|                | p = 0.002    | p = 0.011 | p = 0.008 | p = 0.009 | p = 0.437 |

*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 bidirectional.[8], 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-Mansfield [29], 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. 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 caregivers [30] and was found to be associated with deterioration of the relationship quality in a previous study using MAASBED [31], 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. 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.

**Contributors** – EYLT: researched and analysed the data, wrote the manuscript. MEV: reviewed/edited the manuscript, contributed to the discussion. KD: researched and analysed the data, reviewed/edited the manuscript. JMG: reviewed/edited the manuscript, contributed to the discussion. FRJV: reviewed/edited the manuscript, contributed to the discussion.

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**Competing interests** – None declared.

**Patient consent** - Written informed consent was obtained from all participants before participating in the study.

**Ethics approval** - The study was approved by The Medical Ethics Committee of the University Hospital Maastricht (METC 99-127).

**Patient consent for publication** – Not required.

**Data sharing statement** - Data are available upon reasonable request.

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Figure 1: Mean hyperactivity score on the NPI by EE-group
Figure 2: Mean hyperactivity score on the NPI by EE subgroups critical vs. non-critical
Supplementary figure 1: Lost to follow-up

T0: 112
   - 8 lost to follow-up
     - 3 death
     - 5 other

T1: 104
   - 9 lost to follow-up
     - 6 death
     - 3 other

T2: 95
   - 13 lost to follow-up
     - 10 death
     - 3 other

T3: 82
   - 17 lost to follow-up
     - 7 death
     - 10 other

T4: 65
### 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 |

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 |

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.
| Section/Topic       | Item # | Recommendation                                                                                     | Reported on page # |
|---------------------|--------|---------------------------------------------------------------------------------------------------|-------------------|
| **Title and abstract** | 1      | *(a) Indicate the study's design with a commonly used term in the title or the abstract*            | 1                 |
|                     |        | *(b) Provide in the abstract an informative and balanced summary of what was done and what was found* |                   |
| **Introduction**    | 2      | Explain the scientific background and rationale for the investigation being reported                 | 4,5               |
| **Methods**         | 3      | State specific objectives, including any pre-specified hypotheses                                    | 5                 |
| Study design        | 4      | Present key elements of study design early in the paper                                              | 5                 |
| Setting             | 5      | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5                 |
| Participants        | 6      | *(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants* | 5                 |
|                     |        | *(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and number of controls per case* |                   |
| Variables           | 7      | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5,6,7             |
| Data sources/ measurement | 8*  | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 5,6,7             |
| Bias                | 9      | Describe any efforts to address potential sources of bias                                             | 6                 |
| Study size          | 10     | Explain how the study size was arrived at                                                            | 8                 |
| Quantitative variables | 11    | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 7                 |
| Statistical methods | 12     | *(a) Describe all statistical methods, including those used to control for confounding*              | 7                 |
|                     |        | *(b) Describe any methods used to examine subgroups and interactions*                                | 7                 |
|                     |        | *(c) Explain how missing data were addressed*                                                       |                   |
|                     |        | *(d) Cohort study—if applicable, explain how loss to follow-up was addressed*                       |                   |
|                     |        | Case-control study—if applicable, explain how matching of cases and controls was addressed           |                   |
| Section                                                                 | Suggested Information                                                                                                                                  |
|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses  |
| Results                                                                |                                                                                                                                                    |
| Participants                                                          | 13*                                                                                                                                                    |
| (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8                                                                                                                                                    |
| (b) Give reasons for non-participation at each stage                    | 8                                                                                                                                                    |
| (c) Consider use of a flow diagram                                     |                                                                                                                                                    |
| Descriptive data                                                       | 14*                                                                                                                                                    |
| (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8,9                                                                                                                                                    |
| (b) Indicate number of participants with missing data for each variable of interest |                                                                                                                                                    |
| (c) Cohort study—Summarise follow-up time (eg, average and total amount) |                                                                                                                                                    |
| Outcome data                                                          | 15*                                                                                                                                                    |
| Cohort study—Report numbers of outcome events or summary measures over time | 8,9,10,11                                                                                                                                             |
| Case-control study—Report numbers in each exposure category, or summary measures of exposure |                                                                                                                                                    |
| Cross-sectional study—Report numbers of outcome events or summary measures |                                                                                                                                                    |
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| (b) Report category boundaries when continuous variables were categorized |                                                                                                                                                    |
| (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |                                                                                                                                                    |
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| Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 10,11                                                                                                                                                |
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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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

Eva Y.L. Tan1,2, Marjolein E. de Vugt1, Kay Deckers1, Jos M.G.A. Schols1,3, Frans R. J. Verhey1

1Alzheimer Centre Limburg, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, the Netherlands

2Reinier van Arkel Mental Health Institute, ’s-Hertogenbosch, the Netherlands

3Department of Family Medicine and Department of Health Services Research, Caphri, Maastricht, the Netherlands

Correspondence to: Eva Tan; eva.tan@maastrichtuniversity.nl

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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.
Strengths and limitations of this study

- This is a longitudinal cohort study with a relatively large sample size with 2-year follow-up.
- The association between expressed emotions in caregivers and neuropsychiatric symptoms in persons with dementia living at home was examined taking into account multiple confounding factors.
- Factors associated with expressed emotions were explored as well as the association between expressed emotions and institutionalization rate.
- We used the Five-Minute Speech Sample to measure expressed emotions; this is a feasible instrument, but not the gold standard for measuring the level of expressed emotions.
- The level of expressed emotions was only assessed at baseline, therefore we were not able to study possible changes in expressed emotions over time.
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 Lawton [13] 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 EE [15], 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 time [9] 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 study [17] 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 dementia [18], 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 $\chi^2$ 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      |                 |                  |         |
| - Spouse          | 43              | 15               | 0.336   |
| - 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   |

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

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                |         |
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).

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.

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.
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.

**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.

**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 | p = 0.015           | 9.6 vs. 14.6 | 11.7 vs. 16.1 | 11.8 vs. 16.2 | 10.5 vs. 17.4 | 11.1 vs. 12.7 |
| Critical comments: low vs. high | p = 0.002           | 9.6 vs. 16.1 | 11.4 vs. 18.6 | 11.5 vs. 19.4 | 10.4 vs. 22.2 | 10.3 vs. 14.7 |

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 bidirectional [8], 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-Mansfield [29], 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 caregivers [30] and was found to be associated with deterioration of the relationship quality in a previous study using MAASBED [31], 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.

**Contributors** – EYLT: researched and analysed the data, wrote the manuscript. MEV: reviewed/edited the manuscript, contributed to the discussion. KD: researched and analysed the data, reviewed/edited the manuscript. JMAGS: reviewed/edited the manuscript, contributed to the discussion. FRJV: reviewed/edited the manuscript, contributed to the discussion.

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**Competing interests** – None declared.

**Patient consent** - Written informed consent was obtained from all participants before participating in the study.

**Ethics approval** - The study was approved by The Medical Ethics Committee of the University Hospital Maastricht (METC 99-127).

**Patient consent for publication** – Not required.

**Data sharing statement** - Data are available upon reasonable request.

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Figure 1: Mean hyperactivity score on the NPI by EE-group
Figure 2: Mean hyperactivity score on the NPI by EE subgroups critical vs. non-critical.
Supplementary figure 1: Lost to follow-up

- **T0**: 112
  - 8 lost to follow-up
    - 3 death
    - 5 other

- **T1**: 104
  - 9 lost to follow-up
    - 6 death
    - 3 other

- **T2**: 95
  - 13 lost to follow-up
    - 10 death
    - 3 other

- **T3**: 82
  - 17 lost to follow-up
    - 7 death
    - 10 other

- **T4**: 65
### Supplementary Table 1: Spearman's correlations PwD factors

|       | MMSE  | GDS    | IDDD-i | IDDD-p | NPI    | EE     |
|-------|-------|--------|--------|--------|--------|--------|
| MMSE  | 1.0   |        |        |        |        |        |
| GDS   | -0.56 | 1.0    |        |        |        |        |
|       | (<0.001) | |        |        |        |        |
| IDDD-i | 0.25  | -0.33  | 1.0    |        |        |        |
|       | (0.009) | (<0.001) |      |    |        |        |
| IDDD-p | -0.28 | 0.38   | -0.63  | 1.0    |        |        |
|       | (0.002) | (<0.001) | (<0.001) | |        |        |
| 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 |

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

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.
| Section/Topic            | Item # | Recommendation                                                                                                                                                                                                 | Reported on page # |
|-------------------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Title and abstract      | 1      | (a) Indicate the study’s design with a commonly used term in the title or the abstract                                                                                                                          | 1                 |
|                         |        | (b) Provide in the abstract an informative and balanced summary of what was done and what was found                                                                                                            | 2                 |
| Introduction            |        |                                                                                                                                                                                                              |                   |
| Background/rationale    | 2      | Explain the scientific background and rationale for the investigation being reported                                                                                                                            | 4,5               |
| Objectives              | 3      | State specific objectives, including any pre-specified hypotheses                                                                                                                                                | 5                 |
| Methods                 |        |                                                                                                                                                                                                              |                   |
| Study design            | 4      | Present key elements of study design early in the paper                                                                                                                                                        | 5                 |
| Setting                 | 5      | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection                                                                                   | 5                 |
| Participants            | 6      | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants | 5                 |
|                         |        | (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case                                                                 |                   |
| Variables               | 7      | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable                                                                            | 5,6,7             |
| Data sources/ measurement | 8*    | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group                                          | 5,6,7             |
| Bias                    | 9      | Describe any efforts to address potential sources of bias                                                                                                                                                       | 6                 |
| Study size              | 10     | Explain how the study size was arrived at                                                                                                                                                                       | 8                 |
| Quantitative variables  | 11     | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why                                                                                       | 7                 |
| Statistical methods     | 12     | (a) Describe all statistical methods, including those used to control for confounding                                                                                                                            | 7                 |
|                         |        | (b) Describe any methods used to examine subgroups and interactions                                                                                                                                            | 7                 |
|                         |        | (c) Explain how missing data were addressed                                                                                                                                                                    |                   |
|                         |        | (d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed                                                   |                   |
| Results |  |
|---|---|
| Participants | 13* |
| (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8 |
| (b) Give reasons for non-participation at each stage | 8 |
| (c) Consider use of a flow diagram |  |
| Descriptive data | 14* |
| (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8,9 |
| (b) Indicate number of participants with missing data for each variable of interest |  |
| (c) Cohort study—Summarise follow-up time (eg, average and total amount) |  |
| Outcome data | 15* |
| Cohort study—Report numbers of outcome events or summary measures over time | 8,9,10,11 |
| Case-control study—Report numbers in each exposure category, or summary measures of exposure | 8 |
| Cross-sectional study—Report numbers of outcome events or summary measures | 8 |
| Main results | 16 |
| (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 8,9,10,11 |
| (b) Report category boundaries when continuous variables were categorized |  |
| (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |  |
| Other analyses | 17 |
| Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 10,11 |
| Discussion |  |
| Key results | 18 |
| Summarise key results with reference to study objectives | 11 |
| Limitations | 19 |
| Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 12 |
| Interpretation | 20 |
| Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 11,12 |
| Generalisability | 21 |
| Discuss the generalisability (external validity) of the study results | 11,12 |
| Other information |  |
| Funding | 22 |
| Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 13 |

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

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