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# Depressive symptoms and quality of life after screening for cognitive impairment in patients with type 2 diabetes: observations from the Cog-ID cohort study

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## ABSTRACT

**Objectives** To assess changes in depressive symptoms and health-related quality of life (HRQOL) after screening for cognitive impairment in people with type 2 diabetes.

**Design** A prospective cohort study, part of the Cognitive Impairment in Diabetes (Cog-ID) study.

**Setting** Participants were screened for cognitive impairment in primary care. People suspected of cognitive impairment (screen positives) received a standardised evaluation at a memory clinic.

**Participants** Participants ≥70 years with type 2 diabetes were included in Cog-ID between August 2012 and September 2014, the current study includes 179 patients; 39 screen positives with cognitive impairment, 56 screen positives without cognitive impairment and 84 participants not suspected of cognitive impairment during screening (screen negatives).

**Outcome measures** Depressive symptoms and HRQOL assessed with the Center for Epidemiologic Studies Depression Scale (CES-D), 36-Item Short-Form Health Survey, European Quality of Life-5 Dimensions questionnaire and the EuroQol Visual Analogue Scale. Outcomes were assessed before the screening, and 6 and 24 months after screening. An analysis of covariance model was fitted to assess differences in score changes among people diagnosed with cognitive impairment, screen negatives and screen positives without cognitive impairment using a factor group and baseline score as a covariate.

**Results** Of all participants, 60.3% was male, mean age was 76.3±5.0 years, mean diabetes duration 13.0±8.5 years. At screening, participants diagnosed with cognitive impairment had significantly more depressive symptoms and a worse HRQOL than screen negatives. Scores of both groups remained stable over time. Screen positives without cognitive impairment scored between the other two groups at screening, but their depressive symptoms decreased significantly during follow-up (mean CES-D: −3.1 after 6 and −2.1 after 24 months); their HRQOL also tended to improve.

**Conclusions** Depressive symptoms are common in older people with type 2 diabetes. Screening for and a subsequent diagnosis of cognitive impairment will not increase depressive symptoms.

## Strengths and limitations of this study

- ► The use of a comprehensive neuropsychological assessment at the memory clinic to diagnose cognitive impairment.
- ► Outcomes were assessed prior to, 6 months after and 24 months after screening for cognitive impairment.
- ► High response rate: 94% of the surviving participants after 6 months, 89% after 24 months.
- ► Results could not be compared with people with unidentified cognitive impairment that did not participate in our screening programme.
- ► The participation rate of the Cognitive Impairment in Diabetes study was relatively low (18%), results can only be generalised to elderly patients with type 2 diabetes who agree to be screened for cognitive impairment.

## INTRODUCTION

Cognitive impairment in people with type 2 diabetes can result in problems with self-management, treatment adherence and monitoring.[1] In addition, it increases the risk of severe hypoglycaemia.[2 3] Comorbidities, such as cognitive impairment, must be taken into account to provide optimal care for people with type 2 diabetes.[4] It is well known that cognitive impairment often remains unrecognised by physicians. As a result, the prevalence of missed and delayed diagnoses of cognitive impairment is high.[5–7] The American Diabetes Association (ADA) guidelines recommend annual screening for cognitive impairment in older people with diabetes to facilitate patient-centred care aimed at optimising health outcomes and health-related quality of life (HRQOL).[8] No data are available regarding the implementation of this recommendation.

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Outside the field of diabetes, concerns have been raised regarding whole-population screening for cognitive impairment. Arguments commonly used against screening are the lack of a cure, the risk of stigmatisation and the fear that the diagnosis might evoke depressive symptoms or even suicidal thoughts.[8–10] Targeting higher risk groups, such as those with type 2 diabetes, is considered more clinically meaningful, but some of the same concerns may apply. To get the ADA guidelines implemented on a larger scale, it would be beneficial to have insight in possible negative outcomes. It would be particularly interesting to assess the potential impact of screening and a subsequent diagnosis of cognitive impairment on depressive symptoms in elderly with type 2 diabetes. Besides, assessing whether HRQOL is influenced by screening for cognitive impairment could be a good starting point to design targeted interventions for these vulnerable patients.

The Cognitive Impairment in Diabetes (Cog-ID) study aimed to establish a primary care-based screening strategy to detect cognitive impairment in people with type 2 diabetes.[9] The study showed that self-administered cognitive screening tests can be used for this purpose and that the Self-Administered Gerocognitive Examination (SAGE) had the best diagnostic accuracy (negative predictive value of 85%; positive predictive value of 40%) with a memory clinic established diagnosis as a reference standard.[10]

As both the HRQOL and depressive symptoms were assessed prior to screening, after 6 months and after 24 months, the Cog-ID study is ideally suited to assess changes in depressive symptoms and HRQOL after participating in a screening programme for cognitive impairment in older people with type 2 diabetes.

## METHODS

The design of the Cog-ID study has been described previously.[9] In brief, people ≥70 years with type 2 diabetes were invited by their general practitioner (GP) between August 2012 and September 2014. Exclusion criteria were a diagnosis of dementia, a previous memory clinic evaluation or the inability to read or write. After informed consent, participants underwent a stepwise diagnostic procedure as described below.

### Screening

A research physician visited participants at home. First, participants completed HRQOL and depression questionnaires (see below). Thereafter, they completed two self-administered cognitive tests, the Test Your Memory (TYM)[11] and SAGE.[12] Lastly, the research physician, blinded for the HRQOL and depression scores, and for the TYM and SAGE scores, performed an evaluation with a structured interview and the Mini-Mental State Examination.[13] Participants suspected of cognitive impairment based on this evaluation or either of the cognitive tests (TYM <40; SAGE <15) were classified as screen positive and were invited for a memory clinic evaluation. For reasons out of the scope of this article, 30% of the screen negatives were randomly selected and were also invited to the memory clinic.[9]

### Memory clinic

Cognitive impairment, that is, mild cognitive impairment (MCI) or dementia was established by a multidisciplinary team composed of a neurologist and a neuropsychologist, blinded for all results of the screening visit. Dementia was defined as memory impairment and impairment in at least one other cognitive domain (aphasia, apraxia, agnosia, executive functioning) significantly affecting social or occupational functioning compared with the previous level of functioning and not caused by a delirium, according to Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) criteria.[14] MCI was defined as not normal, not demented, with acquired cognitive complaints that could be objectified as a disorder (ie, performance <5th percentile on normative values) by a neuropsychological assessment, with preserved basic activities of daily living.[15] Participants with objective cognitive impairment on neuropsychological testing, but who did not fulfil MCI or dementia criteria were labelled as 'cognition otherwise disturbed' and classified as screen positive patients without cognitive impairment. In most cases, this was due to an absence of accompanying acquired cognitive complaints, which are requested for a diagnosis of MCI or dementia.

### Communicating the results

Screen negatives received a letter indicating that screening had not revealed signs of cognitive impairment. The memory clinic results and treatment advice of the screen positives were sent to the participants' own GP, who was requested to discuss them with the patient. The GP and the participant decided together what actions were necessary. When desirable, further support by the memory clinic was available. When the participant was diagnosed with cognitive impairment, the GP also received advice on how to adjust their patient's diabetes care (online supplementary file 1).

### Follow-up

Participants received follow-up questionnaires to assess depressive symptoms and HRQOL, 6 and 24 months after screening. Their opinion on study participation was also assessed.

### Measures

Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CES-D).[16] A score ≥16 is generally accepted as the cut-off score for the presence of depression.[17]

The 36-Item Short-Form Health Survey (SF-36) is a questionnaire measuring a patient's HRQOL. It consists of eight domains and two summary scales can be calculated: the Physical Component Scale (PCS) and the Mental Component Scale (MCS). Higher scores indicate



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more favourable levels of functioning.[18] The European Quality of Life-5 Dimensions (EQ-5D) covers five dimensions of HRQOL: mobility, self-care, daily activities, pain/discomfort and anxiety/depression.[19] An index value was computed based on a Dutch valuation study,[20] ranging between 0 and 1, where 0 means death and 1 means full health. The EuroQol Visual Analogue Scale (EQ-VAS) is a graded, vertical line ranging from 0 to 100 (worst to best imaginable health state). Participants were asked to mark a point best reflecting their actual health state.

Information about age, sex and educational level was gathered during screening. Information about the participant's medical history, medication use, diabetes duration and laboratory results was collected from the participant's medical record.

### Outcomes

The change from screening to follow-up in the total CES-D, PCS, MCS, and EQ-VAS scores and in the EQ-5D index value, both after six and after 24 months, were the most important outcomes. Secondary outcomes were the change in the SF-36 domain scores.

### Groups

Participants were classified into three groups:

- 'Screen positives with cognitive impairment': participants suspected of cognitive impairment during screening and diagnosed with either MCI or dementia.
- 'Screen negatives without cognitive impairment': participants not suspected of cognitive impairment during screening.
- 'Screen positives without cognitive impairment': participants suspected of cognitive impairment during screening, but not meeting MCI or dementia criteria.

### Statistical analysis

An analysis of variance model has been fitted to compare the groups pairwise, using a factor group (as defined above). An analysis of covariance model has been fitted to assess change from baseline, using a factor group and baseline score as covariate. A $p<0.05$ was considered significant. Statistical analyses were performed using IBM SPSS statistics V.21.

### Missing data

Twelve (7%) sets of questionnaires were missing after 6 months and 25 (15%) after 24 months. Of all the returned baseline and follow-up questionnaires, 1.0% of the CES-D scores were missing, 1.4% EQ-VAS scores, 2.2% EQ-5D scores and 7% of the PCS and MCS scores. Because an incomplete questionnaire could be related to both depression, HRQOL and cognitive function, the missing data could introduce bias. A sensitivity analysis was therefore performed using multiple imputation by predictive mean matching.

### Patient and public involvement

No patients were involved in developing the research question, outcome measures and the overall design of the study.

## RESULTS

### Study population

Out of 225 Cog-ID participants, 107 were suspected of cognitive impairment based on the screening visit (figure 1). All screen positive participants were invited to the memory clinic, 12 (on average 2 years older, more often a woman and living alone) were not willing to attend and were therefore not included in this study. Out of 95 screen positives who visited the memory clinic, 39 were diagnosed with cognitive impairment and 56 did not fulfil MCI or dementia criteria. These 56 screen positives without cognitive impairment included 15 participants who were labelled as 'cognition otherwise disturbed'.

Out of 118 screen negatives, 34 were invited to the memory clinic as part of the random sample and not included in this analysis. This resulted in a study population of 179 participants; 39 with cognitive impairment, 84 screen negatives and 56 screen positives without cognitive impairment. Table 1 describes the patient characteristics.

### Differences at baseline

At screening, participants with cognitive impairment had more depressive symptoms than screen negative participants (table 2, figure 2). Nine (11%) screen negative participants, 12 (22%) screen positive participants without cognitive impairment and 15 (40%) participants with cognitive impairment scored ≥16 on the CES-D, indicative for the presence of depression.

Participants with cognitive impairment scored worse at baseline compared with screen negatives on most HRQOL scores (online supplementary file 2, table 2). All scores of the screen positives without cognitive impairment were between those of the screen negatives and those of participants with cognitive impairment.

### Differences after 6 and 24 months

Time from screening until the memory clinic evaluation ranged between 12 and 126 (median 35) days. The first follow-up questionnaires were sent to all participants 6 months after the screening visit; 54–168 (median 145) days after the memory clinic evaluation. No association was observed between this time interval and mean CES-D and HRQOL scores (data not shown).

Depressive symptoms in screen negatives and in those with cognitive impairment remained quite stable over time. Unlike these two groups, the screen positives without cognitive impairment experienced a significant improvement in depressive symptoms after 6 months, which sustained after 2 years. This change in depressive symptoms differed significantly between the groups.



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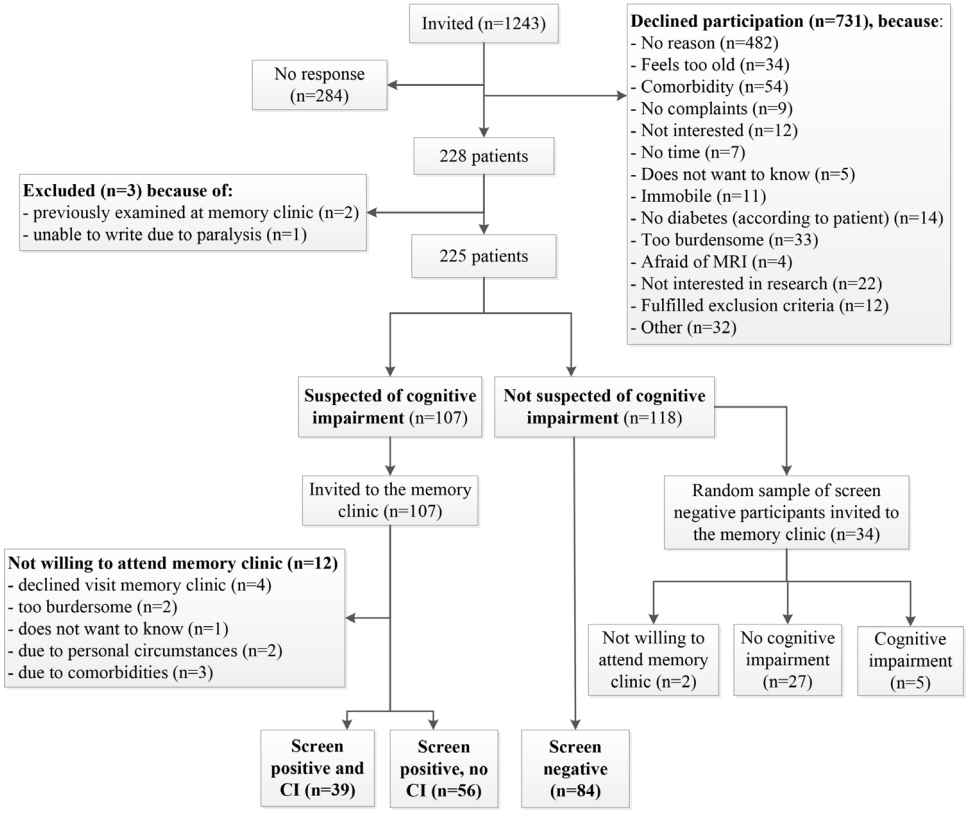


**Figure 1** Patient flow. CI, cognitive impairment.

The change in PCS after 6 months differed between screen negatives and screen positives without cognitive impairment; the PCS improved in the latter (figure 2, table 2).

The sensitivity analysis based on the imputed datasets showed results consistent with the primary analysis (data not shown).

### Patient's opinion on study participation

Six months after screening, 165 (92%) participants completed the question 'do you regret your participation in this study?'. Most (161 (98%)) answered 'no', only four (2%) answered' yes'.

Of the 163 (91%) participants answering the question 'would you be willing to participate again in this study?',

**Table 1** Characteristics of participants at time of screening

| | Total study population, (n=179) | Screen positive and CI (n=39) | Screen positive, no CI (n=56) | Screen negative, (n=84) |
|---|---|---|---|---|
| Age (years) | 76.8±5.0 | 77.7±5.5 | 76.7±4.4 | 76.4±5.2 |
| Female sex | 71 (39.7%) | 17 (43.6%) | 23 (41.1%) | 31 (36.9%) |
| Education* | 4.6±1.4 | 3.9±1.5 | 4.1±1.5 | 5.2±1.1 |
| Diabetes duration (years) | 13.0±8.5 | 14.6±8.6 | 13.5±7.7 | 12.0±8.9 |
| HbA1c (mmol/mol) | 52.8±9.8 | 54.1±9.8 | 52.1±9.2 | 52.7±10.3 |
| HbA1c (%) | 7.0±0.9 | 7.1±0.9 | 6.9±0.8 | 7.0±0.9 |
| Living alone | 70 (39.1%) | 12 (30.8%) | 23 (41.1%) | 35 (41.7%) |
| MMSE | 28.2±2.0 | 26.5±2.9 | 28.3±1.6 | 29.0±1.0 |
| TYME | 40.5±6.7 | 35.3±8.7 | 38.2±6.0 | 44.3±2.6 |
| SAGE | 15.5±4.3 | 11.5±4.3 | 13.5±3.1 | 18.6±2.2 |

Data are presented as means (±SD) or number and proportion in %.
*Educational level is classified by the Dutch Verhage Scale[31]; a seven Point Rating Scale ranging from 1 (which equals a level of less than 6 years of elementary school) to 7 (equals a finished training at a university or technical college).
CI, cognitive impairment; HbA1c, Glycated Hemoglobin; MMSE, Mini-Mental State Examination; SAGE, Self-Administered Gerocognitive Examination; TYME, Test Your Memory.



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Table 2 Depressive symptoms and health-related quality of life scores over time

| | Baseline | | | Mean change after 6 months follow-up | | | | Mean change after 2 years follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screen positive and CI (n=39) | Screen positive, no CI (n=56) | Screen negative, (n=84) | Screen positive and CI (n=39) | Screen positive, no CI (n=56) | Screen negative, (n=84) | | Screen positive and CI (n=39) | Screen positive, no CI (n=56) | Screen negative (n=84) | |
| CES-D | 14.1±7.2 | 12.2±5.2 | 7.1±6.7 | a, b | +0.2±6.1 | −3.1±6.3 | +0.2±5.7 | c | +2.0±7.6 | −2.1±6.1 | +1.0±5.4 | b, c |
| EQ-VAS | 68.2±14.5 | 73.9±13.0 | 76.9±13.1 | a | −4.2±15.5 | −0.7±10.9 | −3.0±10.8 | c | −2.8±15.3 | −3.9±16.7 | −3.5±10.7 | |
| EQ-5D | 0.71±0.27 | 0.81±0.17 | 0.85±0.17 | a, c | −0.01±0.20 | −0.00±0.21 | −0.03±0.16 | | −0.05±0.25 | −0.03±0.22 | −0.01±0.16 | a |
| SF-36: PCS | 48.4±8.1 | 50.2±7.4 | 52.9±8.3 | a | −1.0±6.6 | +1.7±6.2 | −1.6±5.7 | b | −3.2±5.4 | −1.3±7.2 | −3.1±5.7 | |
| SF-36: MCS | 49.4±8.2 | 52.3±7.8 | 53.8±6.4 | a | −2.3±8.2 | −0.6±6.6 | −0.3±6.9 | a | −2.9±9.0 | −2.3±7.4 | −1.1±5.6 | |

Data are presented as means±SD.
a=p<0.05 for difference in (change) score between screen positives with CI and screen negatives.
b=p<0.05 for difference in (change) score between screen positives without CI and screen negatives.
c=p<0.05 for difference in (change) score between screen positives with CI and screen positives without CI.
CES-D, Center for Epidemiologic Studies Depression Scale; CI, cognitive impairment; EQ-VAS, EuroQol Visual Analogue Scale; EQ-5D, European Quality of Life-5 Dimensions; MCS, Mental Component Scale; PCS, Physical Component Scale; SF-36, 36-Item Short-Form Health Survey.

141 (87%) answered 'yes', 22 (13%) 'no'. None of the participants indicated that they would not have wanted to know the results of the study.

## DISCUSSION

### Summary

The present study shows that undiagnosed cognitive impairment in people with type 2 diabetes is associated with depressive symptoms and a reduced HRQOL, already prior to the diagnosis. Yet, neither participating in a screening programme for cognitive impairment nor disclosure of a diagnosis led to a sustained increase in depressive symptoms. In contrast, we found a decrease in depressive symptoms after visiting the memory clinic in screen positives without cognitive impairment. Most HRQOL scores remained stable over time in all participants.

### Interpretation of the results and comparison with existing literature

Depression is about twice as common in people with type 2 diabetes compared with those without.[21] Depression and diabetes are risk factors for one another, and both are associated with an increased risk of cognitive impairment.[22–24] The prevalence of depressive symptoms in our study population was comparable to a Dutch sample of patients with type 2 diabetes, aged 55–85 years.[25] In our study, 40% of patients with cognitive impairment had a CES-D score ≥16, compared with 11% of the screen negative participants and 22% of the screen positive participants without cognitive impairment. These differences are in line with other studies that assessed depressive symptoms in people with cognitive impairment versus those without cognitive impairment, both in the general population[26] and in patients with type 2 diabetes.[27 28] It is thus clear that depressive symptoms, diabetes and cognitive impairment often co-occur, but their relationship is complex and still not completely understood.[22 29] A review of both longitudinal and cross-sectional studies investigating the association between depression and cognitive impairment found evidence to support the assumption that early life depression can act as a risk factor for cognitive impairment, but also that depression can be a prodrome to cognitive impairment.[29] There are also studies suggesting that the relationship between depression and diabetes is bidirectional. The psychological burden of living with a chronic disease could trigger depressive symptoms. Vice versa, depression is associated with a low self-esteem and self-neglect, which could increase the risk of an unhealthy lifestyle and, in turn, the risk of type 2 diabetes.[21] In line with our findings, a previous cross-sectional study in community-dwelling patients, not specifically people with diabetes, reported lower HRQOL scores in participants with cognitive impairments compared with those without. Besides, depressive symptoms were strongly associated with both physical, as well as mental HRQOL.[30] Altogether, the psychological well-being of our study population at



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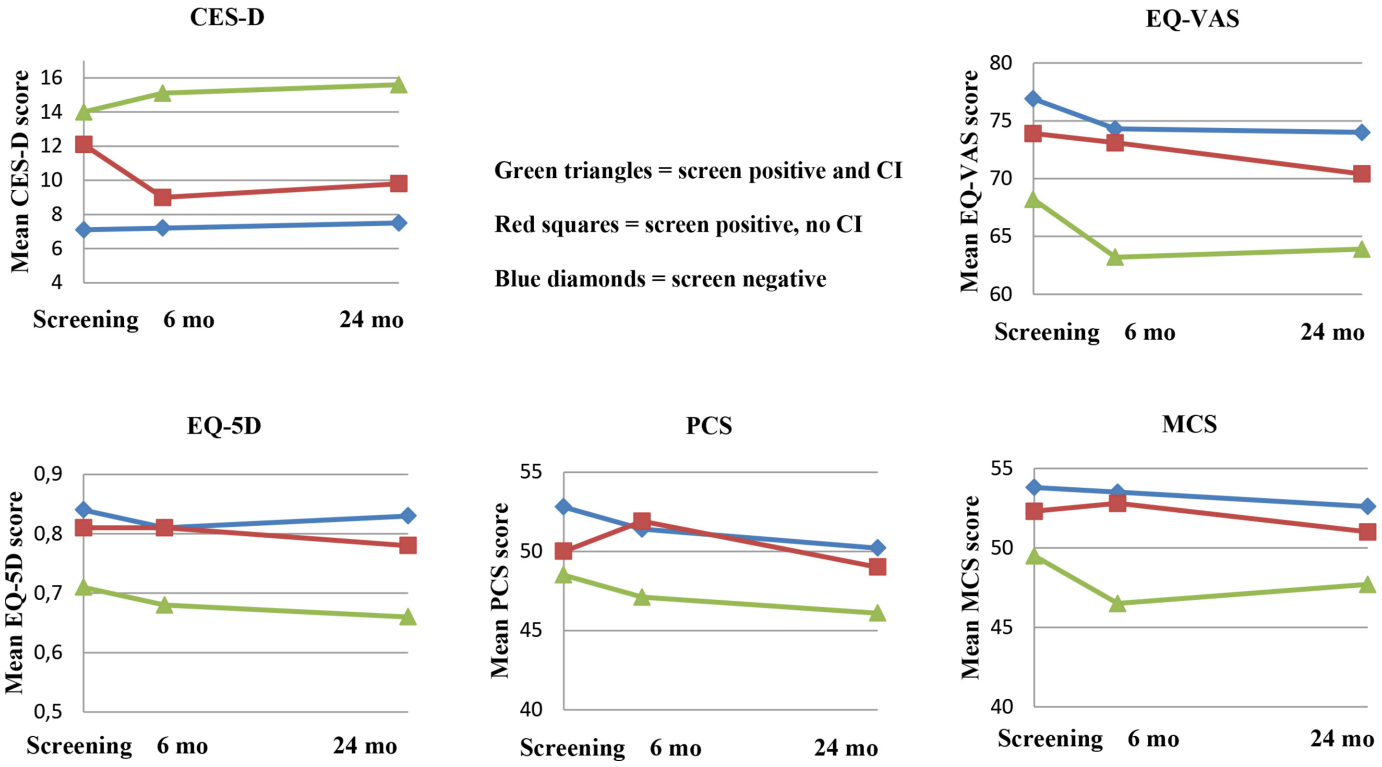


**Figure 2** Depressive symptoms and health-related quality of life scores over time. CES-D, Center for Epidemiologic Studies Depression Scale; CI, cognitive impairment; EQ-VAS, EuroQol Visual Analogue Scale; EQ-5D, European Quality of Life-5 Dimensions; MCS, Mental Component Scale; Mo, month; PCS, Physical Component Scale.

baseline can be considered typical for elderly people with type 2 diabetes who are willing to be screened for cognitive impairment.

Little is known about the impact of screening for cognitive impairment on depressive symptoms and HRQOL, both in people with and in those without diabetes. A systematic review found no studies that addressed the adverse psychological effects from screening for cognitive impairment.[31] A small study published since found no effect of screening on mental health.[32] Qualitative studies indicate that disclosure of a diagnosis of cognitive impairment can be stressful, but it can also end a period of uncertainty and facilitate acceptance and adaptation.[6 33 34] In this study, participating in a screening programme for cognitive impairment did not lead to a sustained increase in depressive symptoms. Besides, none of the participants who received a diagnosis of cognitive impairment indicated afterwards that he or she did not want to know it. These findings support the evidence that fear of inducing depressive symptoms or even suicidal thoughts with the disclosure of a diagnosis of cognitive impairment is unjustified for people who agree to be screened for cognitive impairment.

Surprisingly, we found that depressive symptoms decreased in screen positive participants without cognitive impairment, particularly in the first months after screening. Besides, their HRQOL scores were relatively high after 6 months of follow-up. It could be that the assessment at the memory clinic and its result, indicating that the patient did not have MCI or dementia, decreased depressive symptoms and had a positive effect on the HRQOL. However, we did not find evidence in the literature that depressive symptoms or HRQOL could be improved by reassuring diagnostic results. Another explanation for these findings could be that the depressive symptoms of (a part of) these patients mimicked the symptoms of cognitive impairment during screening. This may have resulted in a high number of depressive symptoms in the group of screen positive participants without cognitive impairment at screening. Either as a result of the natural course or as a result of therapy depressive symptoms may have disappeared during follow-up, with a corresponding improvement of HRQOL scores. Unfortunately, we have not monitored the GP's therapy of the participants' depressive symptoms during the study period.

As discussed in the introduction, the ADA guidelines recommend annual screening for cognitive impairment in older people with diabetes to facilitate patient-centred care aimed at optimising health outcomes and HRQOL.[7] In the present study, HRQOL did not improve after disclosure of a diagnosis of cognitive impairment. In our opinion, optimising HRQOL should not automatically be interpreted as an improvement of HRQOL. Since HRQOL is likely to worsen over the years in the vulnerable group of people with both type 2 diabetes and cognitive impairment,[35 36] less decline in HRQOL might already be positive. However, our findings should be interpreted cautiously, because we were not in the position to compare our results to people who did not participate



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in our screening programme for cognitive impairment and who were unknown with their diagnosis of cognitive impairment.

### Strengths and limitations

A strength of this study is the use of a comprehensive neuropsychological assessment at the memory clinic to diagnose cognitive impairment. The timing of the assessments of depressive symptoms and HRQOL gave us the opportunity to assess these outcomes before they were influenced by the screening programme, relatively short after the programme and in the long term. The response rate for the questionnaires was high (94% of the surviving participants after 6 months, 89% after 24 months), especially considering the vulnerability of this patient group.

As shown in figure 1, the participation rate in the COG-ID study was relatively low (18%). Most frequently mentioned reasons to decline participation were comorbidities, feeling too old and supposing the procedure will be too burdensome. The results of this study can therefore not be generalised to all older people with diabetes, but only to those who are willing to participate in a screening programme for cognitive impairment. This does not hamper its relevance, because diabetes care should be personalised and a screening programme for cognitive impairment will never be obligatory. All memory clinic results and treatment advice were sent to the patients' own GP. The GP was asked to discuss the results with the patient; however, we do not know which actions were actually taken and whether these influenced depressive symptoms and HRQOL. Finally, since only three participants were diagnosed with dementia, we cannot draw any firm conclusions on the effect of disclosure of a diagnosis of dementia.

### Implications for practice

The high prevalence of depressive symptoms and the reduced HRQOL scores in people with type 2 diabetes identified with cognitive impairment indicate that these patients need extra attention. Both cognitive impairment and depressive symptoms in people with type 2 diabetes are associated with reduced self-management skills and increased diabetes-related complications such as hypoglycaemic events.[1 3 37] Early detections of depression and cognitive impairment can facilitate effective treatment and can help to minimise the adverse effects of diabetes management.[38] Ongoing assessment of both cognitive function and depressive symptoms in older people with type 2 diabetes is therefore recommended.[8] Both in the case of depressive symptoms and in case of suspicion of cognitive impairment physicians could tailor the patient's diabetes treatment. Older people are likely to benefit from individualised glycaemic goals and avoidance of overtreatment.[8 39] Harms and benefit of diabetes treatment should be balanced to minimise complications and to optimise well-being.[8] With the growing number of old and very old people with type 2 diabetes, such a policy may become increasingly relevant.

## CONCLUSIONS

Undiagnosed cognitive impairment in patients with type 2 diabetes is associated with a reduced health status and with depressive symptoms. Screening for cognitive impairment in older patients with type 2 diabetes does not seem to affect depressive symptoms or HRQOL negatively. Detection of cognitive impairment identifies a vulnerable patient group that may need extra attention and tailored care.

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**Contributors** PSK, G-JB, JLK and GEHMR designed the study. PSK coordinated the study. PSK and JJ managed the study and data collection. JJ, PSK and G-JB were involved in the data collection. JJ wrote the first manuscript. All authors read, commented and approved the final draft of the manuscript. JJ is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Competing interests** GJB consults for and receives research support from Boehringer Ingelheim and has received speaker's fees from Eli Lily. Compensation for these activities is transferred to his employer, the UMC Utrecht. The other authors report no conflict of interest.

**Patient consent for publication** Not required.

**Ethics approval** The Cog-ID study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO). This study was approved by the medical ethics committee of the University Medical Centre Utrecht, the Netherlands. Written informed consent was obtained from all patients.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** All of the individual participant data collected during the trial, after de-identification, are available to researchers who provide a methodologically sound proposal. The study protocol is available on request.

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