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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 study

Research article

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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

Patients 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 people not suspected of cognitive impairment during screening (screen negatives).

Outcome measures

Depressive symptoms and HRQOL assessed with the Centre for Epidemiologic Studies Depression Scale (CES-D), 36-Item Short-Form Health Survey (SF-36), European Quality of Life-5 Dimensions (EQ-5D) questionnaire and the EuroQol visual analogue scale (EQ-VAS). Outcomes were assessed before screening, and six- and 24 months after screening. An ANCOVA model with factor group and baseline score as covariate was fitted to assess differences in change scores among people diagnosed with cognitive impairment, screen negatives and screen positives without cognitive impairment.

Results

Of all participants, 60.3% was male, mean age was 76.3±5.0 years, mean diabetes duration 13.0±8.5 years. Already at screening, participants diagnosed with cognitive impairment had significantly more depressive symptoms and a worse HRQOL than screen negatives. Scores of both groups remained quite 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 six and -2.1 after 24 months); their HRQOL also tended to improve.

Conclusions

Screening for and a subsequent diagnosis of cognitive impairment do not increase depressive symptoms in older people with type 2 diabetes.

Keywords: cognitive impairment; diabetes; screening; general practice; depression; health related quality of life.

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, six months after and 24 months after screening for cognitive impairment
- High response rate: 94% of the surviving participants after six months, 89% after 24 months
- Results could not be compared to patients with cognitive impairment unknown with their diagnosis that did not participate in our screening program
- The participation rate of the Cog-ID study was relatively low (18%), results can not be generalised to all elderly type 2 diabetes patients

Introduction

Cognitive impairment in people with type 2 diabetes can result in problems with self-management, treatment adherence and monitoring.[1] It also increases the risk of severe hypoglycaemia.[2 3] To provide optimal care, various comorbidities -including cognitive impairment- must be taken into account.[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 6] 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).[7] No data are available about the implementation of this recommendation.

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 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 large scale, it would help 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 provides a unique opportunity to address these issues. The Cog-ID study aimed to establish a procedure to detect undiagnosed cognitive impairment in people with Type 2 diabetes ≥70 years, through screening in a primary care setting, followed by a memory clinic evaluation. Both the HRQOL and depressive symptoms were assessed prior to screening, after six months and after 24 months.

We aimed to assess changes in depressive symptoms and HRQOL after participating in a screening program for cognitive impairment in older people with type 2 diabetes.

Methods

The design of the Cog-ID study has been described previously.[11] 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 write or read. After informed consent participants underwent a stepwise diagnostic procedure as described below.

Screening

Participants were visited at home by a research physician. First, they completed questionnaires assessing HRQOL and depressive symptoms (see below). Then they completed two self-administered cognitive tests, the Test Your Memory (TYM) and Self-Administered Gerocognitive Examination (SAGE).[12] Afterwards, the research physician, blinded for the TYM- and SAGE-scores, performed an evaluation with a structured interview and the Mini-Mental State Examination (MMSE).[13] Participants suspected of CI based on this evaluation or on 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, a random sample of 30% of screen negatives was also invited to the memory clinic.[11]

Memory clinic

Cognitive impairment, i.e. mild cognitive impairment (MCI) or dementia, was established by a multidisciplinary team with a neurologist and a neuropsychologist. 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 to the previous level of functioning and not caused by a delirium, according to DSM-IV criteria.[14] MCI was defined as not normal, not demented, with acquired cognitive complaints that could be objectified as a disorder (i.e. 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'.

In most cases this was due to absence of accompanying acquired cognitive complaints, which are requested for a diagnosis of MCI or dementia.

Communicating the results to the participants

Screen negatives received a letter indicating that screening had not revealed signs of cognitive impairment. The memory clinic results of the screen positives were sent to their GP, who was requested to discuss them with the patient. When the patient was diagnosed with cognitive impairment, the GP also received advice on how to adjust their patient's diabetes care (Supplementary File 1).

Follow-up

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

Measures

Depressive symptoms were assessed with the Centre 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 (PCS) and the mental component scale (MCS). Higher scores indicate 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 participant's medical history, medication use, diabetes duration and laboratory results was collected from the participant's medical record.

Outcomes

Outcome measures were the change from baseline to follow-up in the total CES-D, PCS, MCS, and EQ-VAS scores and the EQ-5D index value, both after six and after 24 months. 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

To compare the groups pairwise, an Analysis of Variance (ANOVA) model has been fitted with factor group. To assess change from baseline, an Analysis of Covariance (ANCOVA) model has been fitted with factor group and baseline score as covariate. A p-value <0.05 was considered significant. Statistical analyses were performed using IBM SPSS statistics 21.

Missing data

Twelve (7%) sets of questionnaires were missing after six months and 25(15%) after 24 months. Of all 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 not completing a 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 to impute missing scores.

Results

Study population

From the 225 Cog-ID participants, 107 were suspected of cognitive impairment based on screening, 118 were not (Figure 1). All screen positives were invited to the memory clinic, twelve (on average two years older, more often woman and living alone) were not willing to attend and therefore not included in this analysis. Of the 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 labelled as 'cognition otherwise disturbed'.

From the 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

Already at screening, participants with cognitive impairment had more depressive symptoms than screen negative participants (Table 2, Figure 2). Nine (11%) of the screen negative participants, twelve (22%) of the screen positive participants without cognitive impairment and fifteen (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 to screen negatives on most HRQOL scores (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 six and 24 months

Time from screening until the memory clinic evaluation ranged between 12-126 (median 35) days. The first follow-up questionnaires were sent to all participants six 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 six months, which sustained after two years. This change in depressive symptoms differed significantly between the groups. The change in PCS after six 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?', 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 more depressive symptoms and a reduced HRQOL, already prior to the diagnosis. Yet, neither participating in a screening program 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 quite stable over time in all participants.

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 program, relatively short after the program, and on the long term. The response rate for the questionnaires was high (94% of the surviving participants after six months, 89% after 24 months), especially considering the vulnerability of this patient group.

As shown in Fig. 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 program for cognitive impairment. This does not hamper its relevance, because diabetes care should be personalised and a screening program for cognitive impairment will never be obligatory. 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.

Comparison with existing literature

The observation that people with undiagnosed cognitive impairment are more likely to suffer from depressive symptoms and a reduced HRQOL compared to those without cognitive impairment is in line with previous studies.[21-24] However, little is known about the impact of screening 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.[25] A small study published since found no effect of screening on mental health.[26] 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.[27 28]

Implications for practice

We did not observe an increase in depressive symptoms after disclosure of the diagnosis cognitive impairment in patients with type 2 diabetes. Normally, depressive symptoms tend to increase slightly with age, probably even more in those with diabetes and cognitive impairment.[29 30] We may therefore assume that this screening program for cognitive impairment and a subsequent diagnosis of cognitive impairment did not affect depressive symptoms negatively. 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 disclosure of a diagnosis of cognitive impairment is unjustified. Surprisingly, we did find 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 six 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. Another explanation for these findings could be that the depressive symptoms of (part of) these patients mimicked the symptoms of cognitive impairment during screening. Since depressive symptoms tend to resolve over

time, this may have led to a decrease of depressive symptoms during follow-up, with a corresponding improvement of HRQOL scores.

In the present study, HRQOL did not improve after disclosure of a diagnosis of cognitive impairment. In our opinion, optimizing HRQOL, as aimed by the ADA recommendation to screen for cognitive impairment, should not be interpreted as improvement of HRQOL. Assuming that HRQOL is likely to worsen over the years in the vulnerable group of people with both Type 2 diabetes and cognitive impairment, less decline in HRQOL might already be positive. We were not in the position to compare our results to people who did not participate in our screening program for cognitive impairment and who were unknown with their diagnosis of cognitive impairment. As stated by the ADA diagnosing cognitive impairment can facilitate patient-centred care. We provided the participating GPs with six noncommittal advices on how to adjust their patients' treatment. A more comprehensive and active intervention might be needed to actually stimulate physicians to personalise diabetes treatment.

Conclusions

No negative effects on depressive symptoms or HRQOL were observed in older patients with type 2 diabetes that participated in a screening program for cognitive impairment.

Acknowledgments

We thank all patients and the general practices that participated in the Cog-ID study.

Regulation statement and ethical 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.

Conflict of interest statement

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.

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Data sharing statement

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

Author contributions

PSK, GJB, LJK and GEHMR designed the study. PSK coordinated the study. PSK and JJ managed the study and data collection. JJ, PSK, and GJB 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.

Members of the Cog-ID study group of University Medical Centre Utrecht

Jolien Janssen, Paula S. Koekkoek, Minke Kooistra, and Guy E.H.M. Rutten from the Julius Centre for Health Sciences and Primary care; Geert Jan Biessels, L. Jaap Kappelle, Esther van den Berg, J. Matthijs Biesbroek and Onno Groeneveld from the Neurology department.

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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 (± standard deviation), or number and proportion in %. CI, Cognitive Impairment.
*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 six years of elementary school) to 7 (equals a finished training at a university or technical college)

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

	Baseline				Mean change after 6 mo. follow-up				Mean change after 2 yr. 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	

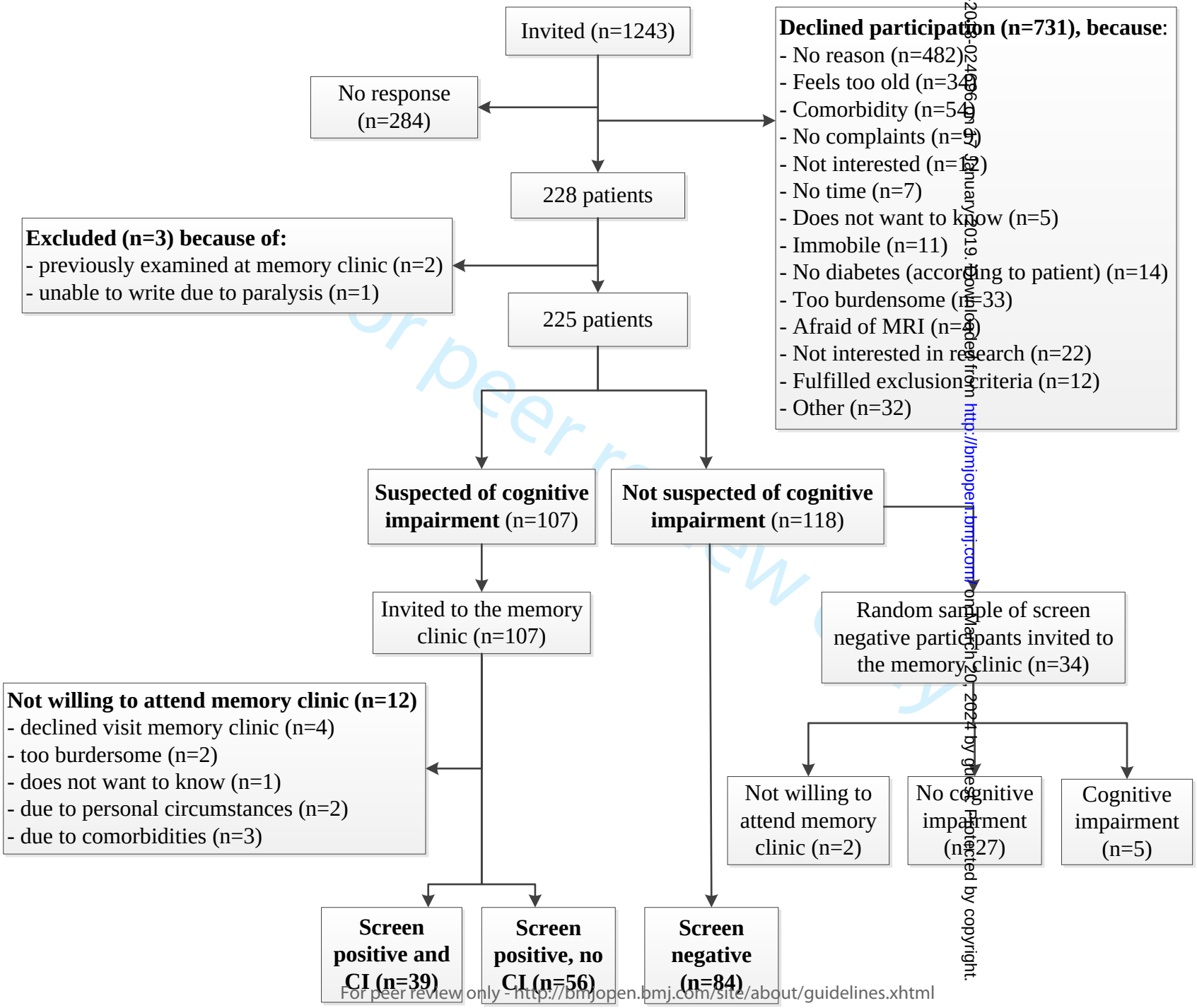
Data are presented as means ± standard deviation. CI, Cognitive Impairment.
a = $p < 0.05$ for difference in (change) score between screen positives with CI and screen negatives.
b = $p < 0.05$ for difference in (change) score between screen positives without CI and screen negatives.
c = $p < 0.05$ for difference in (change) score between screen positives with CI and screen positives without CI.

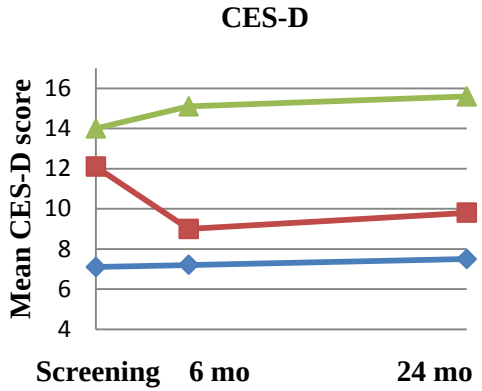
Figure 1 – Patient flow

CI, Cognitive Impairment.

Figure 2 – Depressive symptoms and health related quality of life scores over time

CI, Cognitive Impairment.

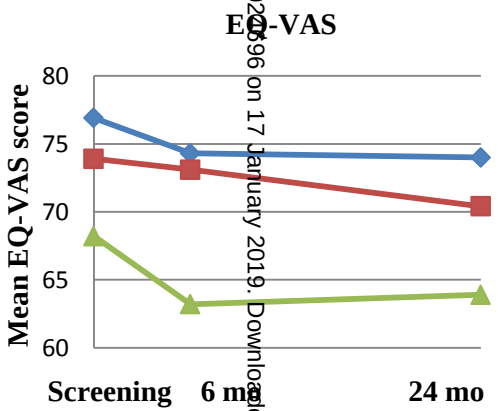


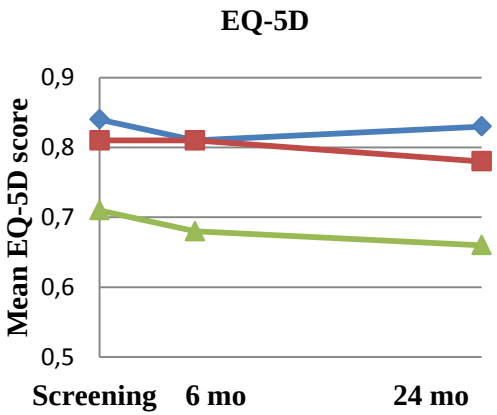


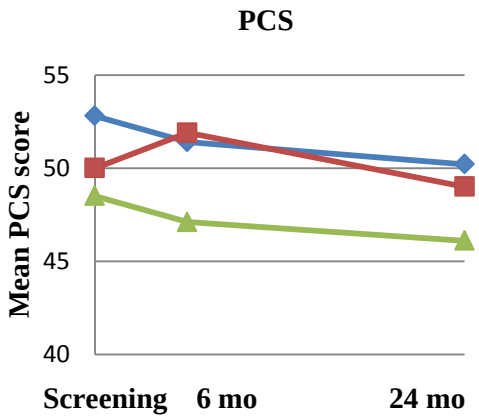
Green triangles = screen positive and CI

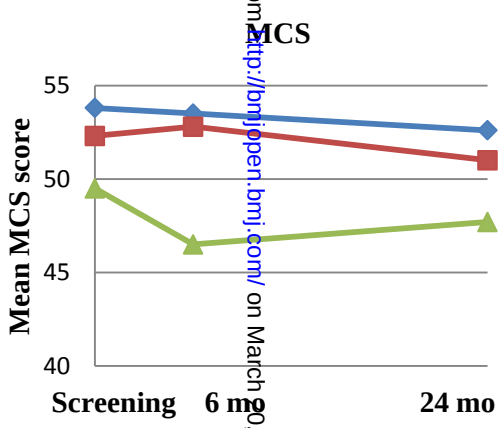
Red squares = screen positive, no CI

Blue diamonds = screen negative









Supplementary File 1– Advice provided to the general practitioners of people diagnosed with MCI or dementia

Subject	Advice
HbA1c target	Strict glycaemic control is associated with hypoglycaemic events and associated falls. This risk is even higher in people with cognitive impairment. A beneficial effect of strict glycaemic control HbA1c < 8% (64 mmol/mol) in older people and those with a long duration of diabetes is not proven. An HbA1c target around 8% (64 mmol/mol) is probably best.
Prevention of hypoglycaemic events	The risk of hypoglycaemic events is higher when insulin is used, adequate use of insulin is more difficult than taking oral medication, perhaps you can replace insulin by an oral drug.
Medication adherence	The use of blister packing makes it easier for people with diabetes to use multiple drugs safely, in people with cognitive impairment this might be even more important.
Hyperglycaemia	If HbA1c is >10.4% (90 mmol/mol) and the patient experiences symptoms which could be due to hyperglycaemia you can explore how to support the patient with his or her treatment or to simplify the treatment.
Cardiovascular risk factors	Treat other cardiovascular risk factors according to corresponding guidelines, but take into account that patient's compliance can be affected.
Reminders	Patients may forget instructions and appointments; it might help to provide notes or written instructions.

Supplementary File 2– SF-36 domain scores over time

	Baseline				**Mean change after 6 mo follow-up**				**Mean change after 2 yr follow-up**			
SF-36 domains:	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)	
Physical functioning	52.4 ±28.1	60.5±24.0	72.0±25.1	a, b	-0.4±13.4	+2.3±15.5	-7.2±14.0	b	-8.2±16.9	-8.2 ±23.4	-10.4 ±14.2	
Role limitations due to physical problems	50.6±40.8	66.9±39.2	75.0±36.6	a	-4.4±31.1	-1.0±54.1	-8.2 ±35.0		-9.2±36.8	-17.4±45.0	-16.4±38.3	
Bodily Pain	69.2±26.0	71.7±25.1	75.9±22.1		-5.7±20.8	+7.7±24.2	-0.2 ±18.9	c	-5.0 ±24.7	-1.8 ±26.6	-3.7 ±21.1	
General Health	54.9±17.6	56.0±16.8	61.5±19.8		-1.9±32.3	+4.3±14.9	-1.3±17.1		-5.3 ±15.9	-0.1±19.6	-2.7±14.1	
Vitality	57.8±22.3	63.5±17.6	71.4±16.9	a	-4.5±13.6	-0.3±16.6	-3.8 ±16.9		-7.0 ±19.3	-6.5 ±20.0	-7.3 ±13.4	
Social functioning	73.7±19.4	78.1±21.0	84.4±16.5	a	-5.4±15.8	+0.9 ±21.3	-1.4±20.3		-10.3±22.7	-12.0±28.3	-6.3±20.9	
Role limitations due to emotional problems	66.7±40.8	80.0±36.1	87.6±27.9	a	-2.0±43.4	+0.7 ±41.8	-3.5±34.4		-8.0±45.1	-7.4±38.2	-3.9±24.8	
Mental Health	74.1±16.1	80.3±14.7	82.2±12.9	a	-6.8±15.1	-0.2±14.8	-0.6 ±10.7	a	-3.0 ±15.9	-0.1 ±19.6	-2.7 ±14.1	

Data are presented as means ± standard deviation.
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.

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

	Item No	Recommendation	Page number
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	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
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	5,6
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	5,6
		(*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	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	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	7,8
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	-
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	8

Continued on next page

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, fig.1
		(b) Give reasons for non-participation at each stage	8, fig.1
		(c) Consider use of a flow diagram	Fig.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table.1
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*Table 2*
		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	
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	Table 2
		(*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	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
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	10
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.

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

Research article

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Figures 2, Tables 2, Supplementary files 2

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 Centre for Epidemiologic Studies Depression Scale (CES-D), 36-Item Short-Form Health Survey (SF-36), European Quality of Life-5 Dimensions (EQ-5D) questionnaire and the EuroQol visual analogue scale (EQ-VAS). Outcomes were assessed before screening, and six- and 24 months after screening. An ANCOVA 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 covariate.

Results

Of all participants, 60.3% is 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 six 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.

Keywords: cognitive impairment; diabetes; screening; general practice; depression; health related quality of life.

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, six months after and 24 months after screening for cognitive impairment
- High response rate: 94% of the surviving participants after six months, 89% after 24 months
- Results could not be compared to people with unidentified cognitive impairment that did not participate in our screening program
- The participation rate of the Cog-ID study was relatively low (18%), results can only be generalised to elderly type 2 diabetes patients 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 is available regarding the implementation of this recommendation.

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 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 six 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 program 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 Self-Administered Gerocognitive Examination (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 (MMSE).[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, i.e. 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 to the previous level of functioning and not caused by a delirium, according to DSM-IV criteria.[14] MCI was defined as not normal, not demented, with acquired cognitive

complaints that could be objectified as a disorder (i.e. 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 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 (Supplementary File 1).

Follow-up

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

Measures

Depressive symptoms were assessed with the Centre 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 (PCS) and the mental component scale (MCS). Higher scores indicate 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 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 (ANOVA) model has been fitted to compare the groups pairwise, using a factor group (as defined above). An Analysis of Covariance (ANCOVA) model has been fitted to assess change

from baseline, using a factor group and baseline score as covariate. A p-value <0.05 was considered significant. Statistical analyses were performed using IBM SPSS statistics 21.

Missing data

Twelve (7%) sets of questionnaires were missing after six 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 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, twelve (on average two years older, more often 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, twelve (22%) screen positive participants without cognitive impairment and fifteen (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 to screen negatives on most HRQOL scores (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 six and 24 months

Time from screening until the memory clinic evaluation ranged between 12-126 (median 35) days. The first follow-up questionnaires were sent to all participants six 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 six months, which sustained after two years. This change in depressive symptoms differed significantly between the groups. The change in PCS after six 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?', 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 program 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 to 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 type 2 diabetes patients, aged 55-85 years.[25] In our study 40% of patients with cognitive impairment had a CES-D score ≥16, compared to 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 relation 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 to those without. Besides, depressive symptoms were strongly associated with both physical, as well as mental HRQOL.[30] Altogether, the psychological wellbeing of our study population at 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 program for cognitive impairment did not led 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 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 six 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 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 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 in our screening program 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 program, relatively short after the program, and in the long term. The response rate for the questionnaires was high (94% of the surviving participants after six months, 89% after 24 months), especially considering the vulnerability of this patient group.

As shown in Fig. 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 program for cognitive impairment. This does not hamper its relevance, because diabetes care should be personalised and a screening program 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 hypoglycemic events.[1;3;37] Early detection of depression and cognitive impairment can facilitate effective treatment and can help to minimise 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 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 wellbeing.[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.

Acknowledgments

We thank all patients and the general practices that participated in the Cog-ID study.

Regulation statement and ethical 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.

Conflict of interest statement

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.

Funding

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Data sharing statement

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

Author contributions

PSK, GJB, LJK and GEHMR designed the study. PSK coordinated the study. PSK and JJ managed the study and data collection. JJ, PSK, and GJB 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.

Members of the Cog-ID study group of University Medical Centre Utrecht

Jolien Janssen, Paula S. Koekkoek, Minke Kooistra, and Guy E.H.M. Rutten from the Julius Centre for Health Sciences and Primary care; Geert Jan Biessels, L. Jaap Kappelle, Esther van den Berg, J. Matthijs Biesbroek and Onno Groeneveld from the Neurology department.

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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 (± standard deviation), or number and proportion in %. CI, Cognitive Impairment.
*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 six years of elementary school) to 7 (equals a finished training at a university or technical college)

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

	Baseline				Mean change after 6 mo. follow-up				Mean change after 2 yr. 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 ± standard deviation. CI, Cognitive Impairment.
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.

Figure 1 – Patient flow

CI, Cognitive Impairment.

Figure 2 – Depressive symptoms and health related quality of life scores over time

CI, Cognitive Impairment.

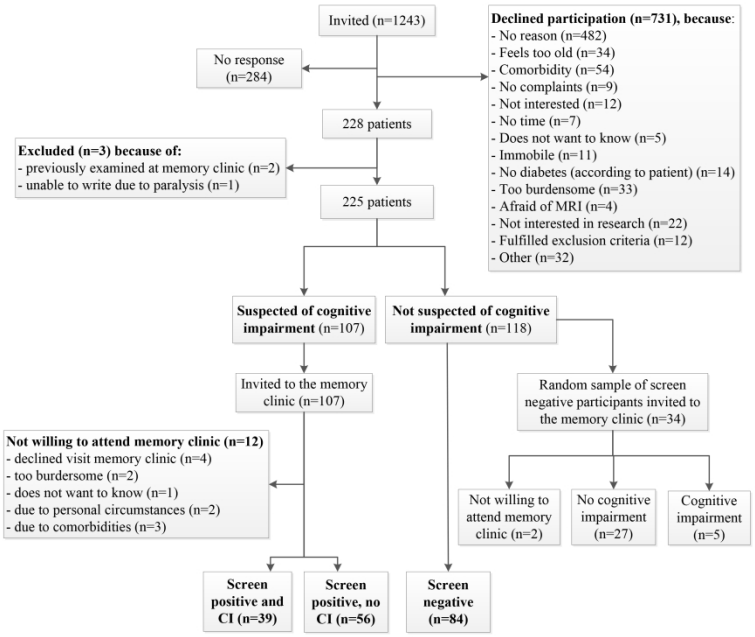

Figure 1 – Patient flow

297x210mm (300 x 300 DPI)

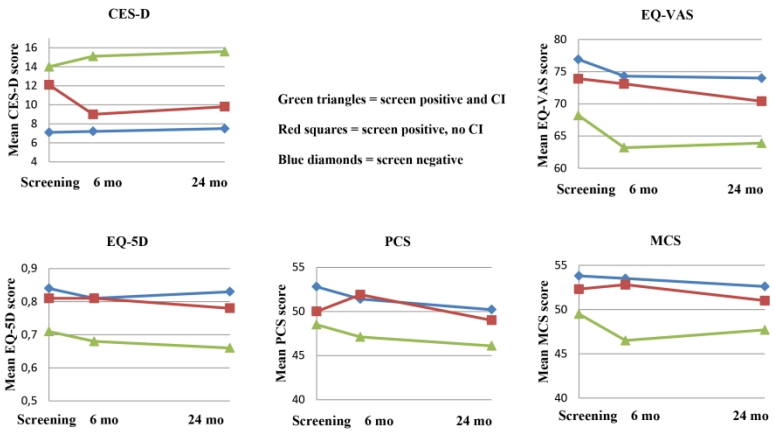

Figure 2 – Depressive symptoms and health related quality of life scores over time

/ CI = cognitive impairment

279x215mm (300 x 300 DPI)

Supplementary File 1– Advice provided to the general practitioners of people diagnosed with MCI or dementia

Subject	Advice
HbA1c target	Strict glycaemic control is associated with hypoglycaemic events and associated falls. This risk is even higher in people with cognitive impairment. A beneficial effect of strict glycaemic control HbA1c < 8% (64 mmol/mol) in older people and those with a long duration of diabetes is not proven. An HbA1c target around 8% (64 mmol/mol) is probably best.
Prevention of hypoglycaemic events	The risk of hypoglycaemic events is higher when insulin is used, adequate use of insulin is more difficult than taking oral medication, perhaps you can replace insulin by an oral drug.
Medication adherence	The use of blister packing makes it easier for people with diabetes to use multiple drugs safely, in people with cognitive impairment this might be even more important.
Hyperglycaemia	If HbA1c is >10.4% (90 mmol/mol) and the patient experiences symptoms which could be due to hyperglycaemia you can explore how to support the patient with his or her treatment or to simplify the treatment.
Cardiovascular risk factors	Treat other cardiovascular risk factors according to corresponding guidelines, but take into account that patient's compliance can be affected.
Reminders	Patients may forget instructions and appointments; it might help to provide notes or written instructions.

Supplementary File 2– SF-36 domain scores over time

	Baseline				Mean change after 6 mo follow-up				Mean change after 2 yr follow-up			
SF-36 domains:	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)	
Physical functioning	52.4 ±28.1	60.5±24.0	72.0±25.1	a, b	-0.4±13.4	+2.3±15.5	-7.2±14.0	b	-8.2±16.9	-8.2 ±23.4	-10.4 ±14.2	
Role limitations due to physical problems	50.6±40.8	66.9±39.2	75.0±36.6	a	-4.4±31.1	-1.0±54.1	-8.2 ±35.0		-9.2±36.8	-17.4±45.0	-16.4±38.3	
Bodily Pain	69.2±26.0	71.7±25.1	75.9±22.1		-5.7±20.8	+7.7±24.2	-0.2 ±18.9	c	-5.0 ±24.7	-1.8 ±26.6	-3.7 ±21.1	
General Health	54.9±17.6	56.0±16.8	61.5±19.8		-1.9±32.3	+4.3±14.9	-1.3±17.1		-5.3 ±15.9	-0.1±19.6	-2.7±14.1	
Vitality	57.8±22.3	63.5±17.6	71.4±16.9	a	-4.5±13.6	-0.3±16.6	-3.8 ±16.9		-7.0 ±19.3	-6.5 ±20.0	-7.3 ±13.4	
Social functioning	73.7±19.4	78.1±21.0	84.4±16.5	a	-5.4±15.8	+0.9 ±21.3	-1.4±20.3		-10.3±22.7	-12.0±28.3	-6.3±20.9	
Role limitations due to emotional problems	66.7±40.8	80.0±36.1	87.6±27.9	a	-2.0±43.4	+0.7 ±41.8	-3.5±34.4		-8.0±45.1	-7.4±38.2	-3.9±24.8	
Mental Health	74.1±16.1	80.3±14.7	82.2±12.9	a	-6.8±15.1	-0.2±14.8	-0.6 ±10.7	a	-3.0 ±15.9	-0.1 ±19.6	-2.7 ±14.1	

Data are presented as means ± standard deviation.
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.

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

	Item No	Recommendation	Page number
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	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
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	5,6
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	5,6
		(*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	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	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	7,8
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	-
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	8

Continued on next page

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, fig.1
		(b) Give reasons for non-participation at each stage	8, fig.1
		(c) Consider use of a flow diagram	Fig.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table.1
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*Table 2*
		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	
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	Table 2
		(*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	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
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	10
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.