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# Cohort Profile: Cohort Hip and Cohort Knee (CHECK) study

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## Abstract

The Cohort Hip and Cohort Knee (CHECK) study included participants with early symptomatic osteoarthritis (OA) of the hip or knee and evaluated clinical, radiographic and biochemical variables in order to establish the course, prognosis and underlying mechanisms of early symptomatic osteoarthritis. A total of 1002 participants aged 45–65 years, with symptomatic OA characterized by pain of knee and/ or hip, entered the cohort in the period October 2002 to September 2005. They were included at or within 6 months of their first visit to the general practitioner for these symptoms. An overview of measures that are included in the study can be found on the website [www.check-research.com]. On the basis of their presenting symptoms, participants were divided into two groups. Participants with mild symptoms visited the research centre at years 0, 2, 5, 8 and 10 (variable visiting group) and participants with more serious symptoms visited the research centre each year (annual visiting group). After 7 years, only 105 participants (10%) had dropped out; their baseline characteristics did not differ significantly from those of other participants. CHECK is a valuable source of information on early symptomatic OA, that allows the examination of high-quality data on clinical, radiographic and biochemical variables. The CHECK steering group welcomes collaboration with national and international colleagues. Requests for collaboration or access to data can be sent to [checkreu@umcutrecht.nl].

**Key Messages**

- CHECK is an inception cohort study of clinical, radiographic and biochemical variables in early symptomatic OA of the hip or knee.
- Preliminary analyses suggest the existence of several clinical and radiographic phenotypes.
- The assessed biochemical markers at baseline were insufficiently discriminating to be used as diagnostic or prognostic markers.
- The study provides a valuable data set to answer many longitudinal research questions regarding OA of the hip or knee.

## Why was the cohort set up?

The course of clinical symptoms and radiographic changes, prognosis and underlying mechanisms of osteoarthritis (OA) is poorly understood, despite the fact that it is the most common diagnosis in older patients with knee and hip pain. For instance, a systematic review summarized the available evidence on predictive factors for the course of hip OA, and concluded that prospective cohort studies with an adequate follow-up time were missing to strengthen the conclusions.[1] In a study on radiological progression of knee OA, it became clear that further work is also needed in the selection and detection of subjects with poor prognosis.[2] From the perspective of prevention and early intervention, it is important to diagnose the disease at an early stage and recognize its prognostic signs. To address the many gaps in this area, the Dutch Arthritis Foundation (DAF) initiated and funded an inception cohort of early symptomatic osteoarthritis (OA) of the hip or knee with 10-year follow-up: CHECK (Cohort Hip and Cohort Knee).

CHECK set out to study clinical, biochemical and radiographic signs and symptoms of early OA, to identify prognostic factors for diagnosis and progression and to study the underlying mechanisms that may cause these symptoms.

An obvious side product of the study is the creation of a Dutch infrastructure for studying osteoarthritis. CHECK offers the possibility to add spin-off studies that require access to CHECK participants (whether from a single clinical centre or from the entire cohort) to collect measurements or data that are not part of the core protocol. At present, 15 spin-off studies have been added to CHECK. We give a few examples of these spin-off studies.

One study investigated the association between baseline hip shape assessed on radiographs, and both clinical hip OA and total hip replacement at 5-year follow-up.[3] Another spin-off study evaluated whether pentosidine can predict radiographic progression and burden of OA over 5 years of follow-up. One of the major age-related changes in cartilage is the accumulation of advanced glycation end-products (AGE). Since cartilage tissue is not readily available from subjects for studying these AGE-levels, skin pentosidine may be used as a surrogate marker for cartilage pentosidine. In this study, all 300 participants of three participating centres were asked for a skin biopsy from the lower back.[4,5] In another spin-off study, the aim was to assess the validity of the avoidance model which is a combined psychological and neuromuscular model to explain clinical characteristics of OA. All CHECK participants recruited through Reade, Centre for Rehabilitation and Rheumatology in Amsterdam, were invited for additional measurements (muscle strength and a performance-based measure of activity limitation).[6]

## Who is in the cohort?

From October 2002 until September 2005, a cohort was formed of 1002 participants. Ten general and university hospitals in The Netherlands are participating, located in semi-urbanized regions. Box 1 lists the inclusion and exclusion criteria. General practitioners near the participating centres were invited to refer eligible persons to these centres. Additionally, participants were recruited through advertisements and articles in local newspapers and on the Dutch Arthritis Foundation website. Most CHECK participants were recruited by advertisements or articles in newspaper (69%), 6% by their physicians, 12% by flyer/family/friend, 12% not recorded. Medical ethics committees of all participating centres approved the study, and all participants gave written informed consent.

## How often have they been followed up?

After inclusion, participants were divided into two groups on the basis of their presenting symptoms (Box 2). Participants in the annual visiting group (with more serious symptoms) visited the research centre each year; participants in the variable visiting group (with mild symptoms) visited the research centre at years 0, 2, 5, 8 and 10. Participants in the variable visiting group were shifted to

**Box 1.** The eligibility criteria of CHECK

Inclusion criteria:

- Pain of knee and/or hip
- Age 45–65 years
- At or within 6 months of first visit to the general practitioner for these symptoms

Exclusion criteria:

- Any other pathological condition that could explain the symptoms (e.g. Other rheumatic disease, previous hip or knee joint replacement, congenital dysplasia, osteochondritis dissecans, intra-articular fractures, septic arthritis, perthes' disease, ligament or meniscus damage, plica syndrome, baker's cyst)
- Comorbidity precluding physical evaluation and/or follow-up of at least 10 years
- Malignancy in the past 5 years
- Inability to understand the Dutch language

**Box 2.** Subgroup criteria of knee and hip, used to divide participants into the variable or annual visiting group

Criteria of knee:

- Knee pain
- Morning stiffness <30 min
- Crepitus
- Bony tenderness

Criteria of hip:

- Hip pain
- Morning stiffness <60 min
- Pain on hip internal rotation or internal rotation <15°

Annual visiting group: participants fulfil two or more of criteria for the hip or knee

Variable visiting group: participants fulfil only one criterion for the hip and only one of the criteria for the knee

the annual visiting group when they met the criteria for that group. At baseline, 861 participants were classified into the annual visiting group and 141 into the variable group; after 2 years 50 participants, and after 5 years another 29 participants, were shifted to the annual visiting group (Figure 1).

After 7 years, 105 participants had been lost to follow-up. Reasons comprised loss of motivation (21%), serious comorbidity (18%), death (12%), loss of contact (11%), costs incurred (5%) and other (33%—including death of partner, move out of the area and unduly burdensome). Apart from 1 year's difference in mean age, there were no statistically significant differences in baseline characteristics between dropouts and participants who were still participating at year 7 (Table 1).

## What has been measured?

Data collection includes clinical, radiological and biochemical data.[2] A coordinator visits the centres every 3 months to check and support complete and accurate data gathering.

### Clinical variables

Clinical assessment comprises self-reported questionnaires, medical history questions and physical examination (clinical features of hips, knees and hands) by a trained health professional. Self-reported questionnaires evaluate hip and knee symptoms,[7,8] hand symptoms,[9] pain severity,[10] coping,[11] health-related quality of life, [12–14] leisure activities and employment,[15] economic consequences,[16] social support[17] and comorbidities[18] (Table 2).

### Radiographic variables

Severity of knee and hip osteoarthritis is scored according to Kellgren and Lawrence (KL; 0–4 scale)[19] on the posterior-anterior radiograph of the knee and the anterior-posterior radiograph of the pelvis. Separate features of the knee and hip are scored on other radiographs according to

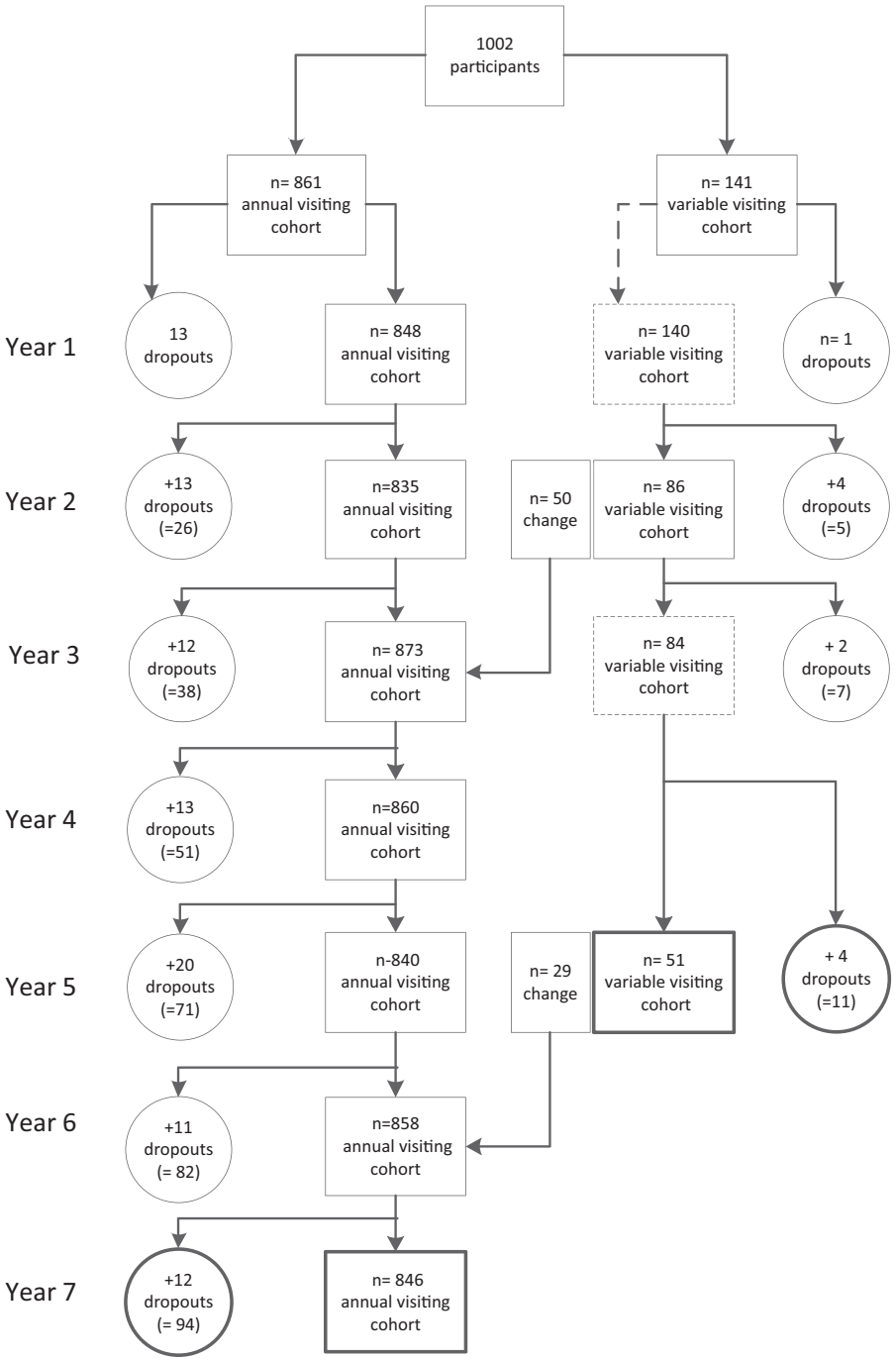


**Figure 1.** Flowchart of the CHECK study.

Altman *et al.*[20] and the radiographic atlas of Burnett *et al.*,[21] both on a 0–3 scale. These radiographs are independently scored by five trained observers. Readers score all consecutive radiographs at the same time with known sequence, but blinded to the clinical status. Interobserver variability was tested in a subset of 38 participants scored by all five observers, yielding moderate to substantial interobserver agreement (*kappa* 0.60 for presence of KL 0 vs KL 1–2–3 in the knees, and *kappa* 0.67 for presence of KL 0 vs KL 1–2–3 in the hips, mean kappas over three measurements: T0–T2–T5).[22] Knee Images Digital Analysis (KIDA) assesses more detailed quantitative parameters on radiographs.[23] These KIDA parameters are measured without knowing the sequence of the radiographs.

## Biochemical variables

Blood and urine samples have been collected from each participant following a standardized protocol at all sites. Multiple aliquots of serum, plasma and urine are centrally

**Table 1.** Comparison of baseline characteristics between people still participating after 7 years of follow-up and those who dropped out

| Characteristics | Subjects participating | Dropouts | *P*-value | 95% confidence interval |
|---|---|---|---|---|
| Number | 897 | 105 | | |
| Age | 56 (5) | 57 (6) | 0.05 | −2.1–0.004 |
| Sex, female, % | 79 | 81 | 0.70 | |
| BMI | 26 (4) | 26 (4) | 0.23 | −0.3–1.4 |
| Education level: | | | 0.58 | |
| • Primary school,% | 2 | 4 | | |
| • Secondary school, % | 60 | 61 | | |
| • High professional education/university, | 35 | 31 | | |
| • Missing, % | 3 | 4 | | |
| WOMAC subscales: | | | | |
| • Pain (0–20) | 5 (3) | 5 (4) | 0.19 | −1.2–0.2 |
| • Stiffness (0–8) | 3 (2) | 3 (2) | 0.86 | −0.4–0.3 |
| • Function (0–68) | 16 (11) | 17 (14) | 0.19 | −4.0–0.8 |
| Pain intensity (0–10) | 4 (2) | 4 (2) | 0.96 | −0.4–0.4 |
| Hip pain, % | 59 | 57 | 0.79 | |
| Knee pain, % | 83 | 82 | 0.75 | |
| Highest KL score knee | | | 0.89 | |
| • Grade 0, % | 68 | 66 | | |
| • Grade 1, % | 25 | 26 | | |
| • Grade 2, % | 6 | 8 | | |
| • Grade 3, % | 1 | 1 | | |
| • Missing | 1 | 0 | | |
| Highest KL score hip | | | 0.74 | |
| • Grade 0, % | 79 | 78 | | |
| • Grade 1, % | 14 | 17 | | |
| • Grade 2, % | 5 | 4 | | |
| • Grade 3, % | 1 | 1 | | |
| • Missing, % | 1 | | | |
| Comorbidities | | | 0.23 | |
| • 0, % | 31 | 37 | | |
| • 1,% | 30 | 27 | | |
| • 2, % | 20 | 12 | | |
| • ≥3, % | 17 | 20 | | |
| • Missing, % | 2 | 4 | | |

Continuous variables are given as mean values, standard deviation between brackets and categorical variables as percentages.

BMI, body mass index; KL, Kellgren and Lawrence grade; WOMAC, Western Ontario and McMaster Universities OA index with higher scores indicating worse health

stored at −80°C. DNA was collected at baseline and was stored at −20°C. A systematic review of the currently available biochemical markers in knee and hip OA was the basis for composing the spectrum of biochemical markers to be assessed at baseline in the CHECK study: uCTX-II, uCTX-I, uNTX-I, sCOMP, sPIIANP, sCS846, sC1, 2C, sOC, sPINP, sHA, sPIIINO, pLeptin, pAdiponectin, pResistin (Table 3).[24]

## What has it found? Key findings and publications

An actual list of publications can be found on our website [www.check-research.com]. Here we summarize the key findings.

### Clinical variables

The course of pain and physical function in patients with early symptomatic OA remains, on average, fairly stable over 5 years, especially in participants with a slow progression (radiographic change of 0 or 1 grade in KL grading). In participants with a rapid progression (radiographic change of ≥2 in KL grading), pain increased and function declined. Already in an early stage of the disease, large inter-individual differences appear in the course of activity limitations and pain,[25] which is in concordance with the literature.[26] Based on 5 years' data of activity limitations, homogeneous subgroups of subjects were identified with comparable trajectories of activity limitations: 'good',

**Table 2.** Summary of collected data during 10 years in all participants (all) and in the subgroup of the annual visiting group (A) of CHECK

| | Year | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Questionnaires | | | | | | | | | | | |
| • Demographics | all | A | all | A | A | all | A | A | all | A | all |
| • SF-36: Short Form 36-item health status survey | all | A | all | A | A | all | A | A | all | A | all |
| • EQ5D: EuroQol | all | A | all | A | A | all | A | A | all | A | all |
| • WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index | all | A | all | A | A | all | A | A | all | A | all |
| • NRS for pain intensity (numerical rating scale) | all | A | all | A | A | all | A | A | all | A | all |
| • Comorbidity list | all | A | all | A | A | all | A | A | all | A | all |
| • Health care use | all | A | all | A | A | all | A | A | all | A | all |
| • Pain Coping Inventory list | all | | all | | | all | | | all | | all |
| • Social Support scale | all | | all | | | all | | | all | | all |
| • Lifestyle: tobacco and alcohol use | all | | all | | | all | | | all | | all |
| • AUSCAN: Australian Canadian Osteoarthritis Hand Index | | | | | | | | | all | | |
| • ICOAP: Measure of Intermittent and Constant Osteoarthritis Pain | | | | | | | | | all | A | all |
| Clinical assessment | | | | | | | | | | | |
| Knee examination | all | A | all | A | A | all | A | A | all | A | all |
| ■ Palpable warmth<br>■ Refill test<br>■ Bony tenderness<br>■ Patella grinding test<br>■ Range of motion—flexion/ extension<br>■ Crepitus | | | | | | | | | | | |
| Hip examination | all | A | all | A | A | all | A | A | all | A | all |
| ■ Range of motion—flexion/internal/ External rotation / adduction/abduction | | | | | | | | | | | |
| Hand examination | | | | | | | | | | | |
| ■ DIP/PIP bony enlargements | all | A | all | A | A | all | A | A | all | A | all |
| ■ CMC I bony enlargements | | | | | | | A | A | all | A | all |
| ■ Soft-tissue swelling MCP I-V | | | | | | | A | A | all | A | all |
| ■ Deformity CMC I, DIP, PIP | | | | | | | A | A | all | A | all |
| Radiographic assessment | | | | | | | | | | | |
| • Knee: unilateral posterior-anterior fixed flexion view (both knees) | all | | all | | | all | | | all | | all |
| • Knee: unilateral lateral view (both knees) | all | | all | | | all | | | all | | all |
| • Knee: bilateral skyline view (supine) | all | | all | | | all | | | all | | |
| • Hip: anterior-posterior pelvis view | all | | all | | | all | | | all | | all |
| • Hip: unilateral faux profile view (both hips) | all | | all | | | all | | | | | |
| • Hand: bilateral posterior-anterior view | | | | | | | | | all | | |
| • Lumbar spine: lateral view (supine) | | | | | | | | | all | | |
| Biochemical assessment | | | | | | | | | | | |
| • DNA | all | | | | | | | | | | |
| • Plasma | all | | all | | | all | | | all | | |
| • Serum | all | | all | | | all | | | all | | |
| • Urine | all | | all | | | all | | | all | | |

'moderate' and 'poor outcome'.[27] The following baseline characteristics distinguished poor and moderate outcome from good outcome: younger age, higher BMI, greater pain, bony tenderness, reduced knee flexion, hip pain, osteophytes on X-rays, three or more comorbidities and lower or avoidance of activity. Distinguishing these baseline characteristics might have implications for treatment.

A combined psychological and neuromuscular model was developed to explain clinical characteristics of OA. According to this model, a person experiences pain during activities, expects renewed activities to result in more pain and consequently avoids activities. In the long term, inactivity results in muscle weakness that leads to an increase in activity limitations.[28,29] In patients with early-stage OA,

**Table 3.** Description of biomarkers

| Category biochemical marker | Biomarker | Description biomarker |
|---|---|---|
| Cartilage degradation | CTX-II | C-terminal telopeptide of type II collagen |
| | sC1, 2C | Collagen of types I and II |
| | sCOMP | Cartilage oligomeric matrix protein |
| Cartilage synthesis | sPIIANP | Collagen N-propeptide of type IIA |
| | sCS846 | Chondroitin sulphate 846 |
| Bone degradation | uCTX-I | C-terminal telopeptide of collagen I |
| | uNTX-I | N-terminal telopeptide of collagen I. |
| Bone synthesis | sOC | Osteocalcin |
| | sPINP | Aminoterminal propeptide of type I procollagen |
| Synovium degradation | sHA | Hyaluronic acid |
| Synovium synthesis | sPIIINP | N-terminal propeptide of type III procollagen |
| Adipokines | pLeptin | |
| | pAdiponectin | |
| | pResistin | |

this model appears to offer a valid explanation for the associations between pain, negative affect (i.e. feeling of fatigue, low vitality, depression and nervousness), avoidance of activities, muscle weakness and activity limitations.[6]

At baseline, 67% of participants reported one or more comorbidities. Additional problems in the musculoskeletal system (apart from knee and hip problems) and obesity have a negative effect on pain and physical health status. Mental health status is also affected in early symptomatic OA by the presence of specific comorbidities.

Besides the course of pain and activity limitations, the course of work participation was analysed also. The 2-year course of work participation was similar to that of the general Dutch population. Sustained work participation was predicted by lower age, not by OA-related factors.[30]

### Radiographic variables

The gold standards to evaluate radiographic OA are KL grading and grading according to the Altman atlas. The newer method, KIDA, appeared sensitive in detecting early progression of radiographic knee damage, especially through the measurement of separate quantitative features of radiographic knee OA.[31] Based on KIDA features, five phenotypes of radiographic progression can be identified. These represent the level of disease progression (Severe or No progression), the phase of progression (Early or Late) and the prominent involvement of Bone density.[32]

Statistical Shape Modelling (SSM)assessed the radiographic shape of the hip, to test whether the morphology of the hip joint could be a risk factor for OA. Evaluation of the hip radiographs of CHECK participants showed that the SSM-modelled shape of the hip can predict total hip replacement, but variation in shape cannot predict clinical OA.[3] In addition, individuals with severe cam-type deformity (hip incongruity by non-spherical head) and reduced internal rotation were at high risk of fast progression to end-stage OA.[33] Finally, pincer deformity (acetabulum over-coverage) did not lead to OA of the hip, but acetabulum under-coverage did.[34]

### Biochemical variables

In CHECK, 14 markers of cartilage, bone and synovial metabolism (Table 3) were assessed to improve understanding of pathophysiology and as potential prognostic predictors. None proved sufficiently discriminating to predict diagnosis or prognosis of OA. Two reflected a broader spectrum than expected. The cartilage degradation marker, CTX-II, showed striking similarities with markers of bone metabolism, suggesting that CTX-II also originates from bone. The cartilage degradation marker COMP (Cartilage Oligomeric Matrix Protein) may also originate from (inflamed) synovial tissue in early-stage OA.[35] Biomarkers confirmed cartilage degradation and synovitis as processes underlying the development of radiographic signs in early-stage knee and hip OA. Markers of bone turnover and bone mineral density suggest that these are relevant factors in the development of radiographic OA, but their effects may differ between knee and hip.

## What are the main strengths and weaknesses?

CHECK's main strength is the combination of high-quality data in the clinical, radiographic and biochemical domains. Second, CHECK is an inception cohort: observations started at the same point in the course of OA in all

participants. Third, CHECK has a follow-up of 10 years and thereby provides a huge data set to answer longitudinal research questions on OA of the hip or knee. Fourth, CHECK has a remarkably low loss to follow-up, due to a special retention programme.

This programme is aimed at optimizing the compliance of CHECK participants and motivating health professionals involved in the participating hospitals (physicians, researchers, X-ray technicians, research nurses). Activities include: twice-yearly newsletters for participants and health professionals, separate websites for participants and health professionals, organizing symposia for both groups to present preliminary results and progress of CHECK, and sending birthday cards to all participants.

The main weakness of the study is related to the fact that no diagnostic criteria of early OA exist; this may hamper generalizing results. CHECK participants are subjects with early OA, defined as having pain in hip or knee at or within 6 months of their first visit to the general practitioner for these symptoms, and complaints were not attributable to another rheumatic disease. There are however criteria for OA; 76% of the CHECK participants with knee pain fulfilled the clinical American College of Rheumatology classification criteria for knee OA and 24% fulfilled the clinical classification criteria of hip OA. These criteria for OA were developed in cases of established disease. None of the CHECK participants had radiographic OA (i.e. KL grade $\geq$2). The transition from early to established OA is gradual. That is why we decided to call the situation at presentation 'symptomatic OA'.

## Can I get hold of the data? Where can I find out more?

The CHECK steering group welcomes collaboration and the interest of national and international colleagues. More information on CHECK can be found on [www.check-research.com], and from [http://www.check-research.com/images/upload/english/spin-offformulierENG.doc] a sign-up form can be downloaded to describe a proposal for collaboration or a request for access to data, to be sent to [checkreu@umcutrecht.nl]. The CHECK steering committee will evaluate all proposals for spin-off studies, for access to data and for use of biological samples.

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## Author contributions

J.W., M.B., M.V., W.H., F.L., J.D. and J.B. contributed to conception and design of this study. J.W. contributed to the analysis of data. M.B., M.V., W.H., F.L., J.D. and J.B. contributed to the interpretation of data. Article drafts were written by J.W. and critically revised by all authors. The final version of the article was approved by all authors. J.W. takes responsibility for the integrity of the work as a whole [j.wesseling@umcutrecht.nl].

**Conflict of interest:** None declared.

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