## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands |
| **AUTHORS** | Castelijns, Maria; Helmink, Marga; Hageman, Steven; Asselbergs, Folkert; de Borst, Gert-Jan; Bots, Michiel; cramer, maarten jan; Dorresteijn, Jannick; Emmelot-Vonk, Marielle; Geerlings, Mirjam I; de Jong, P. A.; van der Kaaij, Niels; Kappelle, Jaap; Lely, Titia; van der Meer, Manon; Mol, Barend; Nathoe, Hendrik; Onland-Moret, N. Charlotte; van Petersen, Rutger; Ruigrok, Ynte; van Smeden, Maarten; Teraa, Martin; Vandersteen, Angela; Verhaar, Marianne; Westerink, Jan; Visseren, Frank |

## VERSION 1 – REVIEW

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| **REVIEWER** | Saif Al-Shamsi<br>United Arab Emirates University College of Medicine and Health Sciences, Internal Medicine |
| **REVIEW RETURNED** | 19-Sep-2022 |

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| **GENERAL COMMENTS** | Thank you for the opportunity to review the manuscript, “Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in The Netherlands” by Castelijns M, et al.<br><br>This single-center study included over 14,000 patients from the Netherlands. This manuscript provides the reader with an update on the ongoing UCC-SMART study.<br><br>I enjoyed reading this manuscript as it was well-written and the cohort description findings up to date were clear. The strengths of the study include the large sample size and long follow-up period. The authors should be commended on providing the reader with an extensive overview of the study’s design.<br><br>In summary, I would recommend accepting this manuscript for publication. |

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| **REVIEWER** | Bert-Jan van den Born<br>Amsterdam UMC Locatie AMC, Vascular Medicine |
| **REVIEW RETURNED** | 10-Nov-2022 |

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| **GENERAL COMMENTS** | In the present manuscript the authors provide an update of the UCC SMART cohort, a pivotal ongoing cohort study that includes patients at high risk for cardiovascular disease (either based on risk factors |

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| | or incident cardiovascular events) in Utrecht, the Netherlands.<br><br>The rationale for the update is clear and the elaborate discussion of the strengths and limitations of the SMART cohort very useful and important, also because this cohort is at the basis of the cardiovascular risk prediction incorporated in the SMART risk score.<br><br>Major comments<br><br>From the text it remains unclear to what extent the population is representative of the general population. Do patients exclusively belong to the hospital catchment area or are referred patients from other parts of the country also included? If so do they differ in their characteristics?<br><br>In the methods section it appears that abdominal fat mass and perivascular fat is calculated from the abdominal ultrasound. To the best of my knowledge ultrasound generally has limited ability to assess fat mass. What methods were used and what is their validity and/or reproducibility?<br><br>It is stated that SMART will be continuously expanded. However, expansion is not always feasible nor desirable. What is the projected goal with regard to sample size? What type of statistical methods are used for the main outcome analysis?<br><br>The substudies (in bold) are mentioned only briefly. Therefore, it is not always clear what their purpose is in relation to the SMART cohort and whether addition of the substudies in the text adds to the information.<br><br>To what extent do patients who were lost to follow up differ from patients with complete follow-up data?<br><br>Are patient data linked to pharmacy records and if so are changes in medication use and/or uptake recorded in the UCC SMART cohort?<br><br>Minor comments<br><br>In the abstract the figure 14 830 is mentioned twice<br><br>A few sentences can be improved ie ‘to use of their data’ page 6. |

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| **REVIEWER** | Nathalie Conrad<br>KU Leuven, Medical Sciences Division |
| **REVIEW RETURNED** | 06-Dec-2022 |

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| **GENERAL COMMENTS** | In this manuscript, the authors describe the rationale, study design, participants, measurements and findings to date of the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC- SMART) cohort. The UCC-SMART study provides valuable data and resources for future studies to improve understanding of aetiology, prediction and prognosis of cardiovascular disease.<br>In my view, the study design is adequate and well described. Analyses appear to have been performed meticulously and are presented accurately. A detailed description of the UCC- SMART cohort alongside initial findings is important for future studies relying on this resource. I found the manuscript particularly well written and clear, and only have minor comments, which I outline below.<br>1. Author mention that participants with “short life expectancy” were |

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| | excluded. This is a rather vague concept - Could authors please define how this was defined and assessed.<br>2. Authors mention that baseline measurements were taken more than 30 days after the CVD event/risk assessment leading to enrollment – can authors please provide the median/IQR for the time interval between the CVD event/risk assessment and baseline measurements?<br>3. The part where authors describe that the cohort was linked to Statistic Netherlands, which contains data on ICD-10 coded diagnoses and hospital admissions is unclear. Does this mean that the full cohort is linked to electronic health records data from every general practice, specialist, and hospital in the Netherlands? Or just a subset of practices/hospitals? It would be good if authors could clarify.<br>4. Lines 433 and following, authors describe cancer incidence rates, but it is unclear what the denominator is here. Could authors please clarify that and add percentages.<br>5. Table 2, Line 16 on page 23 – it is unclear which outcome event this refers to. |

**VERSION 1 – AUTHOR RESPONSE**

**Reviewer 1 (dr. Saif Al-Shamsi)**

**Thank you for the opportunity to review the manuscript, "Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in The Netherlands" by Castelijns M, et al.**

**This single-center study included over 14,000 patients from the Netherlands. This manuscript provides the reader with an update on the ongoing UCC-SMART study.**

**I enjoyed reading this manuscript as it was well-written and the cohort description findings up to date were clear. The strengths of the study include the large sample size and long follow-up period. The authors should be commended on providing the reader with an extensive overview of the study's design.**

**In summary, I would recommend accepting this manuscript for publication.**

We would like to thank dr. Al-Shamsi for the positive feedback.

**Reviewer 2 (dr. Bert-Jan van den Born)**

**In the present manuscript the authors provide an update of the UCC SMART cohort, a pivotal ongoing cohort study that includes patients at high risk for cardiovascular disease (either based on risk factors or incident cardiovascular events) in Utrecht, the Netherlands.**

**The rationale for the update is clear and the elaborate discussion of the strengths and limitations of the SMART cohort very useful and important, also because this cohort is at the basis of the cardiovascular risk prediction incorporated in the SMART risk score.**

First of all, we want to thank prof. Van den Born for the compliments and valuable comments, which we believe have improved the manuscript.

**Major comments**

1. **From the text it remains unclear to what extent the population is representative of the general population. Do patients exclusively belong to the hospital catchment area or are referred patients from other parts of the country also included? If so do they differ in their characteristics?**

The UMC Utrecht is a university hospital that provides secondary care to patients referred by general practitioners from the catchment area and tertiary care for specific patients groups. However, those patients with specific conditions such as heart transplantation, cardiomyopathy or other rare causes of vascular disease such as vasculitis or connective tissue diseases are not included in UCC-SMART. In the UCC-SMART cohort, patients with or at high risk of cardiovascular disease are included, corresponding to patients with severe cardiovascular risk factors or established CVD from the general population. This is also captured by the inclusion criteria (Supplementary Table 1).

We have clarified this in the section 'Strengths and limitations' of the manuscript: *"Patients included in UCC-SMART correspond to patients with severe cardiovascular risk factors or established CVD from the general population. As reflected by the inclusion criteria, the UCC-SMART study does not include patients requiring highly specialized care (including heart transplantation and rare causes of vascular disease)."* (lines 558-560).

2. **In the methods section it appears that abdominal fat mass and perivascular fat is calculated from the abdominal ultrasound. To the best of my knowledge ultrasound generally has limited ability to assess fat mass. What methods were used and what is their validity and/or reproducibility?**

We would like to thank the reviewer for this comment. In the UCC-SMART study, abdominal ultrasound is used to assess both visceral and subcutaneous adipose tissue thickness. The methods used are described in section 'Radiology testing', lines 210-222. As stated in lines 213-214 and 223, measurements are performed using an EPIQ-7 ultrasound machine (Philips Medical Systems, Eindhoven, The Netherlands).

CT assessment is the gold standard, but not all patients should be subjected to this type of diagnostic technique. Ultrasound measurements are relatively inexpensive and avoid ionizing radiation risks. The correlation with CT-derived volumes and reliability was studied before, showing ultrasound is an accurate method to assess visceral adipose tissue.(1) In both people without obesity and people with a body mass index of 25 kg/m$^2$ or over, correlation between ultrasound measurements of visceral fat and CT measurements was strong ($\rho$ = 0.81-0.89).(2–4) Furthermore, reproducibility of ultrasound measurements was good ($\rho$ = 0.87-0.94) (4,6) which was, amongst others, shown in a study conducted in the UMC Utrecht.(5) Similar results were found for the correlation with MRI measurements (correlation $\rho$ = 0.84-0.90) with low intra- and interobserver errors as well.(5,6)

We have added a phrase and reference about the validity and reproducibility to this section of the manuscript: *"Ultrasonography has been proven a suitable technique to measure intra-abdominal adipose tissue with good reproducibility.[11,12]"* (lines 232-233).

3. **It is stated that SMART will be continuously expanded. However, expansion is not always feasible nor desirable. What is the projected goal with regard to sample size? What type of statistical methods are used for the main outcome analysis?**

We thank the reviewer for this relevant question. The goal is to maintain an up-to-date cohort of patients at high risk of cardiovascular disease, to continue to provide an infrastructure for etiologic, diagnostic, prognostic and therapeutic research. Since some of the patients included in the earliest years of the UCC-SMART study have already died and because health care and insights into risk factors and treatments change over time, ongoing inclusion and follow-up ensure an up-to-date study population. Because the UCC-SMART data is used for various research projects, different subsets are

selected from the cohort for each project, for example only patients with diabetes mellitus or cerebrovascular disease. Therefore, one single sample size calculation cannot be provided.

We have emphasized this in the manuscript in the abstract: *"The UCC-SMART study guarantees an infrastructure for etiologic, diagnostic, prognostic and therapeutic research in high-risk patients. The cohort will continue to include about 600 patients yearly and follow-up will be ongoing to ensure an up-to-date cohort in accordance with current health care and scientific knowledge."* (lines 53-56), and in the section 'Strengths and limitations': *"The UCC-SMART study is a unique ongoing prospective cohort study in over 14,000 patients with a history of various manifestations of CVD or severe cardiovascular risk factors, providing a large up-to-date cohort of a population at high cardiovascular risk."* (lines 520-522).

4. **The substudies (in bold) are mentioned only briefly. Therefore, it is not always clear what their purpose is in relation to the SMART cohort and whether addition of the substudies in the text adds to the information.**

We thank the reviewer for pointing this out. In the substudies, extra information or parameters are collected in subsets of patients, including 1.5T cardiac MRIs (SMART-HEART), 1.5T water-fat MRIs to assess the amount of supraclavicular and subcutaneous adipose tissue, and additional questionnaires about cardiovascular risk factors and CVD in offspring of patients (SMART-Junior). We discuss them briefly to provide an overview of which data is available for future researchers. The references mentioned with the substudies as well as Supplementary Table 6 can be consulted in order to obtain more information about the substudies.

In order to clarify that the substudies provide additional information on top of the 'usual' baseline measurements of SMART, we added this in the section 'Other substudies':

*"Several other substudies have been carried out within the UCC-SMART cohort, providing additional information and parameters for subsets of patients (Supplementary Table 6)."* (lines 373-374).

5. **To what extent do patients who were lost to follow up differ from patients with complete follow-up data?**

We thank the reviewer for this relevant question. In the UCC-SMART study, reasons for follow-up to end in patients who are still alive are either that patients indicated that they no longer wish to participate in further follow-up, or that patients were unreachable for follow-up questionnaires. As stated in the manuscript, the median follow-up time of these patients is 7.4 years (IQR 3.9 – 11.4). We have clarified these reasons in the manuscript in section 'Characteristics of the study population': *"Of those, 3,294 patients died and 89% (n = 10,219) of the surviving patients are still being followed up. Reasons for follow-up to end in surviving patients include withdrawal of participation in further follow-up (80%) or being unreachable for further questionnaires (20%). The median follow-up time of these patients without complete follow-up data is 7.4 years (IQR 3.9 - 11.4)."* (lines 429-434) and in section 'Strengths and limitations': *"Furthermore, in 10.6% of the included patients, follow-up ended due to either withdrawal of participation in further follow-up (8.5%) or being unreachable for further questionnaires (2.1%). Yet, the median follow-up time for these patients is 7.4 years, so those patients still contribute to a fair amount of patient-years."* (lines 551-554).

The table below shows the most important baseline characteristics for patients with complete follow-up data (n = 13,257 [89.4%]) and patients without complete follow-up (n = 1,573 [10.6%]).

| | **Patients with complete follow-up (n = 13,257)** | **Patients without complete follow-up (n = 1,573)** |
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| Age (years) | 57 ± 12 | 55 ± 14 |
| Male sex | 8,736 (66) | 894 (57) |
| Previous or current smoking | 9,285 (70) | 1,065 (69) |
| Established cardiovascular disease | 8,270 (65) | 913 (59) |
| Diabetes mellitus | 2,272 (17) | 336 (22) |
| Lipid-lowering therapy | 7,529 (57) | 724 (47) |
| Antihypertensive therapy | 9,053 (68) | 977 (63) |
| Oral anticoagulant therapy | 1,145 (9) | 121 (8) |
| Systolic blood pressure (mmHg) | 140 ± 22 | 144 ± 23 |
| Diastolic blood pressure (mmHg) | 83 ± 13 | 84 ± 13 |
| Body mass index (kg/m$^2$) | 26.9 ± 4.4 | 27.1 ± 4.8 |
| Non-HDL-cholesterol (mmol/L) | 3.8 ± 1.3 | 4.0 ± 1.5 |
| eGFR (ml/min/1.73 m$^2$) | 53 ± 41 | 48 ± 43 |
| HbA1c (mmol/mol) | 38 (36 - 42) | 40 (36 - 48) |
| CRP (mg/L) | 2.0 (1.0 - 4.3) | 2.2 (1.0 - 4.4) |

*Data are presented as number (percentage), mean ± standard difference or median (interquartile range).*

As can be observed in the table above, patients with and patients without complete follow-up data are quite comparable. We have clarified this in the manuscript in section 'Characteristics of the study population' by adding the following sentence: "*Baseline characteristics of patients with complete follow-up data available were comparable to the characteristics of patients who withdrew from or were unreachable for further follow-up. (Supplementary Table 7).*" (lines 453-455). We also added the table above to the Supplementary Material (Table 7).

6. **Are patient data linked to pharmacy records and if so are changes in medication use and/or uptake recorded in the UCC SMART cohort?**

We thank the reviewer for this question. Information about medication use at baseline is obtained by a questionnaire. Changes in medication use and/or uptake during follow-up are not routinely registered. A future plan is to obtain information on medication use during follow-up by linking the UCC-SMART cohort to the Dutch Foundation for Pharmaceutical Statistics (in Dutch: Stichting Farmaceutische Kengetallen, SFK), gathering data from over 97% of the community pharmacies in the Netherlands.(7)

We have added an additional subheading *"Dutch Foundation for Pharmaceutical Statistics"* to the manuscript section 'Linkage to other registries: *"A future plan is to obtain information on medication use during follow-up by linking the UCC-SMART cohort to the Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK). This foundation obtains data from over 97% of the community pharmacies in the Netherlands.[21]"* (lines 337-340).

**Minor comments**

1. **In the abstract the figure 14 830 is mentioned twice**

We thank the reviewer for this observation.

We removed the second '14,380' from the abstract and replaced it by 'the': *"By May 2022, <u>the</u> included patients contributed to a total follow-up time of over 134,000 person years."* (line 47).

2. **A few sentences can be improved ie 'to use of their data' page 6.**

We want to thank the reviewer for pointing this out. We thoroughly reread the manuscript and corrected textual inaccuracies.

**<u>Reviewer 3 (dr. Nathalie Conrad)</u>**

**In this manuscript, the authors describe the rationale, study design, participants, measurements and findings to date of the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC- SMART) cohort. The UCC-SMART study provides valuable data and resources for future studies to improve understanding of aetiology, prediction and prognosis of cardiovascular disease.**

**In my view, the study design is adequate and well described. Analyses appear to have been performed meticulously and are presented accurately. A detailed description of the UCC-SMART cohort alongside initial findings is important for future studies relying on this resource. I found the manuscript particularly well written and clear, and only have minor comments, which I outline below.**

We appreciate dr. Conrad's positive feedback, we thank her for her insightful comments and we welcome the improvements her comments has led to in our manuscript.

1. **Author mention that participants with "short life expectancy" were excluded. This is a rather vague concept - Could authors please define how this was defined and assessed.**

We thank the reviewer for this question. We agree that 'short life expectancy' is rather vague, however, this is based on the treating physician's opinion. Indeed, the treating physician at the outpatient clinic or hospital ward decides whether the patient could be included in the UCC-SMART study. There are no established criteria by which 'short life expectancy' is defined, but this is mainly based on the age and medical history of the patient, such as metastatic malignancy or advanced neurodegenerative disease.

We have clarified this in Supplementary Table 1: "*short life expectancy (per judgement of the treating physician)".*

2. **Authors mention that baseline measurements were taken more than 30 days after the CVD event/risk assessment leading to enrollment – can authors please provide the median/IQR for the time interval between the CVD event/risk assessment and baseline measurements?**

We thank the reviewer for this question and agree that this could be relevant information. However, the exact date of the inclusion diagnosis is not recorded in the UCC-SMART database. In case of inclusion after an acute CVD event, patients are invited after discharge from the hospital and are included after at least 30 days (in practice often 2-3 months after the event). Since all participants are included at least 30 days after acute CVD events, the UCC-SMART study can be regarded as a cohort of patients with stable cardiovascular disease or severe cardiovascular risk factors.

3. **The part where authors describe that the cohort was linked to Statistic Netherlands, which contains data on ICD-10 coded diagnoses and hospital admissions is unclear. Does this mean that the full cohort is linked to electronic health records data from every general practice, specialist, and hospital in the Netherlands? Or just a subset of practices/hospitals? It would be good if authors could clarify.**

We would like to thank the reviewer for this clarifying question. The Central Agency for Statistics (Statistic Netherlands) collects data from administrative sources of other (government) agencies, such as municipalities for mortality data, and the national medical registration 'Landelijke Basisregistratie Ziekenhuiszorg (LBZ)' of Dutch Hospital Data for ICD-10 codes and hospital admissions. The full UCC-SMART cohort can be linked to the Central Agency for Statistics database containing this data, so it will not be linked to the electronic health records of all general practices and hospitals separately. All Dutch hospitals supply data to Dutch Hospital Data, (8) and information from primary care comes

from general practices affiliated with the healthcare registration 'Nivel Zorgregistraties'. Patients from these participating general practices are a good reflection of the Dutch population.(9)

We have clarified this in the section 'Linkage to external registies' in the manuscript: *"The CBS collects data from all hospitals in the Netherlands and from general practitioner practices affiliated with 'Nivel' healthcare registration, which are a good reflection of the Dutch population.*(8,9)*"* (lines 318-320).

4. **Lines 433 and following, authors describe cancer incidence rates, but it is unclear what the denominator is here. Could authors please clarify that and add percentages.**

We thank the reviewer for pointing out that this was not mentioned in the manuscript. The findings of the entire section ('Findings to date') are reported for patients included up to January 2020 (n = 13,898), because the collection and processing of outcome events has been completed up until this date. Hence, the percentage of patients diagnosed with cancer during follow-up was 15%.

We have clarified this in the 'Findings to date' section by adding '(n = 13,898)': *"The findings of this section are reported for patients included up to January 2020 (n = 13,898),..."* (line 468) and by adding the percentage of patients diagnosed with cancer during follow-up: *"Through linkage with the Dutch National Cancer Registry, a total of 2,139 patients (15%) was diagnosed with cancer during follow-up."* (line 483). To be consistent, we also added percentages to the number of patients with incident diabetes, end-stage kidney disease, heart failure, major bleeding and patients who underwent a vascular intervention: *"Furthermore, there were 943 (7%) cases of incident diabetes, 105 (1%) cases of end-stage kidney disease, 161 (1%) cases of heart failure and 434 (3%) cases of major bleeding. A total of 3,264 (23%) patients underwent a vascular intervention during follow-up."* (lines 473-475).

5. **Table 2, Line 16 on page 23 – it is unclear which outcome event this refers to.**

We thank the reviewer for pointing this out. Unfortunately, something went wrong with inserting the table into the manuscript. We have corrected this so the numbers are now in the right place again.

## VERSION 2 – REVIEW

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| **REVIEWER** | Bert-Jan van den Born<br>Amsterdam UMC Locatie AMC, Vascular Medicine |
| **REVIEW RETURNED** | 03-Jan-2023 |

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| **GENERAL COMMENTS** | The authors have addressed my suggestions and/or comments in an appropriate and satisfactory manner. I have no further questions. |

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| **REVIEWER** | Nathalie Conrad<br>KU Leuven, Medical Sciences Division |
| **REVIEW RETURNED** | 03-Jan-2023 |

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| **GENERAL COMMENTS** | Thank you for revising your manuscript. I am happy with the changes suggested by the authors and recommend the manuscript for publication. |