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ORIGINAL ARTICLE

The Stockholm CREAtinine Measurements (SCREAM) project: protocol overview and regional representativeness

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Abstract

Background: We here describe the construction of the Stockholm CREAtinine Measurement (SCREAM) cohort and assess its coverage/representativeness of the Stockholm county in Sweden. SCREAM has the principal aims to estimate the burden and consequences of chronic kidney disease (CKD) and to identify inappropriate drug use (prescription of nephrotoxic, contraindicated or ill-dosed drugs).

Methods: SCREAM is a repository of laboratory data of individuals, residing or accessing healthcare in the region of Stockholm, who underwent creatinine assessments between 2006–11. Laboratory tests were linked to administrative databases with complete information on socioeconomic status, demographic data, healthcare utilization, diagnoses, vital status and dispensed prescription medicines.

Results: SCREAM identified 1 118 507 adult Stockholm citizens with available creatinine tests between 2006–11. This corresponded to 66% of the complete population in the region. Geographical coverage was uniform, ranging between 62 and 72% throughout its 26 municipalities. Population coverage was higher across older age strata (50% coverage for age range 18–44 years, >75% for 45–64 years and >90% coverage for ≥65 years). Of note, 97 and 98% of all individuals with a diagnosis of diabetes mellitus or cardiovascular disease, respectively, were captured by SCREAM. Further, 89% of all deaths registered in the period occurred in individuals with a creatinine test undertaken.

Conclusion: SCREAM represents the largest cohort to estimate the burden and healthcare implications of CKD in Sweden. The coverage and representativeness of the region of Stockholm was high and in accordance to both the commonness of creatinine

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assessment, and the medical indications for creatinine testing. The inclusion of individuals who sought medical care and had a creatinine test undertaken resulted in a slight over-representation of elderly and comorbid patients.

Key words: chronic kidney disease, creatinine, epidemiology, population

Background

The development of simple creatinine-based equations to estimate kidney function has contributed to raise the epidemics of chronic kidney disease (CKD) to the category of major public health problem [1]. CKD is an important contributor to the burden of non-communicable diseases, leading to poor quality of life and severely reduced life expectancy [2]. CKD also has a substantial impact on societal costs, by increasing per se the need for healthcare services [3] and contributing to work disability [4]. Further, the consequences of CKD are of importance for many other aspects of healthcare, including the incidence of other comorbidities [1, 5] or impairment on the diagnostic accuracy of laboratorial analyses and medical devices [6–8] dependent on protein or fluid retention by the failing kidneys. Notwithstanding that creatinine is a very common and low-cost assessment in healthcare [9, 10], systematic screening programs are lacking and, in most societies, the awareness of CKD among both physicians and patients remains very low [11, 12].

Kidney dysfunction affects, and also is affected by drug metabolism [13]. Many drugs have nephrotoxic effects per se or by forcing hydrophilic drug hyperfiltration in damaged kidneys. Further, significant morbidity is experienced due to medication accumulation and exposure in CKD, commonly leading to adverse events, prolonged length of hospital stay, increased healthcare cost and even death [14, 15], even when drug clearance is mediated by non-renal mechanisms [16]. Drug-induced nephrotoxicity indeed accounts for 25% of episodes of acute kidney injury [17], a figure that can be as high as 70% among the elderly [18]. Due to low CKD awareness, the risk for inappropriate drug utilization (IDU) in the community is high [13, 15, 19–21], representing a likely important risk factor for CKD progression and complications [22, 23].

Sweden is a Northern European country with universal healthcare access and a population of 9.8 million inhabitants as of 2015, with nearly 25% living in the County of Stockholm. The burden of CKD in Sweden, especially of earlier CKD stages, and its impact on society and healthcare utilization is currently unknown. Awareness of the extent of the problem is needed to estimate and plan for allocation of resources on disease prevention strategies as well as diagnosis and early management. Assessment of plasma creatinine is one of the most common routine laboratory analyses performed on wide indications in clinical practice, both in the emergency setting and in regular check-ups of patients with various disorders. The extent of this occasional creatinine testing is unknown, but can provide important information on kidney function in order to inform patients and guide clinical practice. The Stockholm CREAtinine Measurement (SCREAM) project is a collaborative project between Karolinska Institutet and the Stockholm County Council (SLL by Swedish acronym), to ascertain the burden of CKD and the extent of IDU in the region. SCREAM is also linked to an intervention programme to decrease IDU. This article provides an overview of the SCREAM objectives and goals, details of the laboratory data extraction and linked data sources. Further, we also provide an assessment of regional coverage and representativeness.

Overarching objectives of SCREAM

SCREAM objectives are focussed around key research methodologies: clinical epidemiology, health services research, pharmacoepidemiology and health economics. The following four specific aims were initially identified:

(i) To determine the prevalence of CKD in the region of Stockholm, Sweden, and ascertain its clinical consequences in terms of comorbid complications and healthcare resource utilization.
(ii) To determine healthcare- and socioeconomic-related risk factors for progression of CKD.
(iii) To identify IDU in the context of kidney dysfunction (incorrectly dosed or nephrotoxic drug prescription) and to document its adverse clinical consequences.
(iv) To establish the safety and effectiveness of common drugs in individuals with CKD.

Construction and content

Laboratory extraction overview

The core component of SCREAM was a central repository of laboratory data. Three laboratory companies (Aleris, Unilabs and Karolinska) performed the vast majority of all clinical chemistry laboratory tests of the region. Each laboratory provider extracted the requested laboratory tests for all patients who had these measurements undertaken throughout the region. The inclusion criteria considered to enter SCREAM was to be a Stockholm resident with a valid personal identifying number undertaking at least one measurement of creatinine in primary, secondary or tertiary care during 2006–11. All creatinine tests analysed during the period were included, as well as other laboratory measurements routinely linked to CKD and used to guide ongoing patient assessment, monitor disease progression and identify relevant outcomes (Table 1).

Table 1. Routine laboratory tests collected in SCREAM

Serum tests
Creatinine
Cystatin-C
Albumin
Haemoglobin
Haemoglobin A1c
Glucose
C-reactive protein
Parathyroid hormone
Blood lipids: cholesterol, low density lipoprotein- and high density lipoprotein-cholesterol, triglycerides
Electrolytes: K^+, HCO^{3-}, Na^-, Ca^{2+}, PO^{4-}, CO_2^-
Thyroid hormones: thyroid stimulating hormone, triiodothyronine and thyroxine, both total and free
Prothrombin time (international normalized ratio)
Urine tests
Dipstick albuminuria
Albumin-to-creatinine ratio

Each laboratory test included, in addition to the details of the test, a unique patient identifier (Swedish personal identification number [24]), the date on which the test was performed, method used and units of measurement. Concerning serum creatinine, all laboratory providers had since 2005 implemented either enzymatic or corrected Jaffe method (alkaline picrate reaction), both methods being traceable to isotope dilution mass spectroscopy standards. Creatinines analysed locally (on site) were largely included, as most analysing machines were connected to the laboratory data system. Inter- as well as intra-laboratory variation was considered minimal, with the three laboratories being frequently audited for quality and harmonization by the national organization EQUALIS (www.equalis.se). All ages were included in the cohort. However, in the absence of patient data such as height and weight, estimation of kidney function by established equations becomes less accurate for individuals below 18 years of age, and we did not consider them in our analyses.

Management of healthcare utilization data

Patient-identified laboratory data were sent from each laboratory provider to SLL's subcontracted company Tieto Sweden AB (http://www.tieto.se/). The personal identifier was used to link the laboratory data to the administrative health data register of this region (Vårdanalysdatabasen, VAL; Stockholm regional healthcare data warehouse [25]) (Figure 1). VAL is established by SLL and contains information on all consultations in primary and secondary care (defined as specialist outpatient care), as well as hospitalizations. Both public and private healthcare providers within the region report each patient visit to VAL. Data for primary care was available since 2003, and for secondary care and hospitalization since 1993. Each healthcare visit was accompanied by the date (and when applicable discharge date), the centre accessed and medical department, therapeutic procedures undertaken and established diagnoses according to the International Classification of Diseases Version 10 (ICD-10) coding system. Identification of the type of healthcare visit in which the laboratory test was performed is important to differentiate test results obtained during a hospitalization (potentially influenced by acute illness) from those performed in the out-patient setting, which may better reflect stable medical conditions. Comorbid history will be primarily defined based on the disease domains of the Charlson comorbidity score [26, 27]. The presence of one or more diagnostic codes in any position up to 3 years prior to measurement entry will be considered to define comorbidity history.

Patient demographics included sex and date of birth (month and year), migration procedures (when applicable date of registration as county citizen and date of departure/emigration), and ascribed municipality of residency according to the national classification of Statistics Sweden. Information on race is not available in Sweden by law, and in accordance with the general population characteristics, it was assumed that all patients were of Caucasian origin. ICD-10 codes and therapeutic procedures were retrieved for each individual since 1997 and up to 31 December 2012.

Management of national quality registers

The SCREAM dataset was thereafter sent to the National Board of Health and Welfare, to be linked to the following national quality registers [28]:

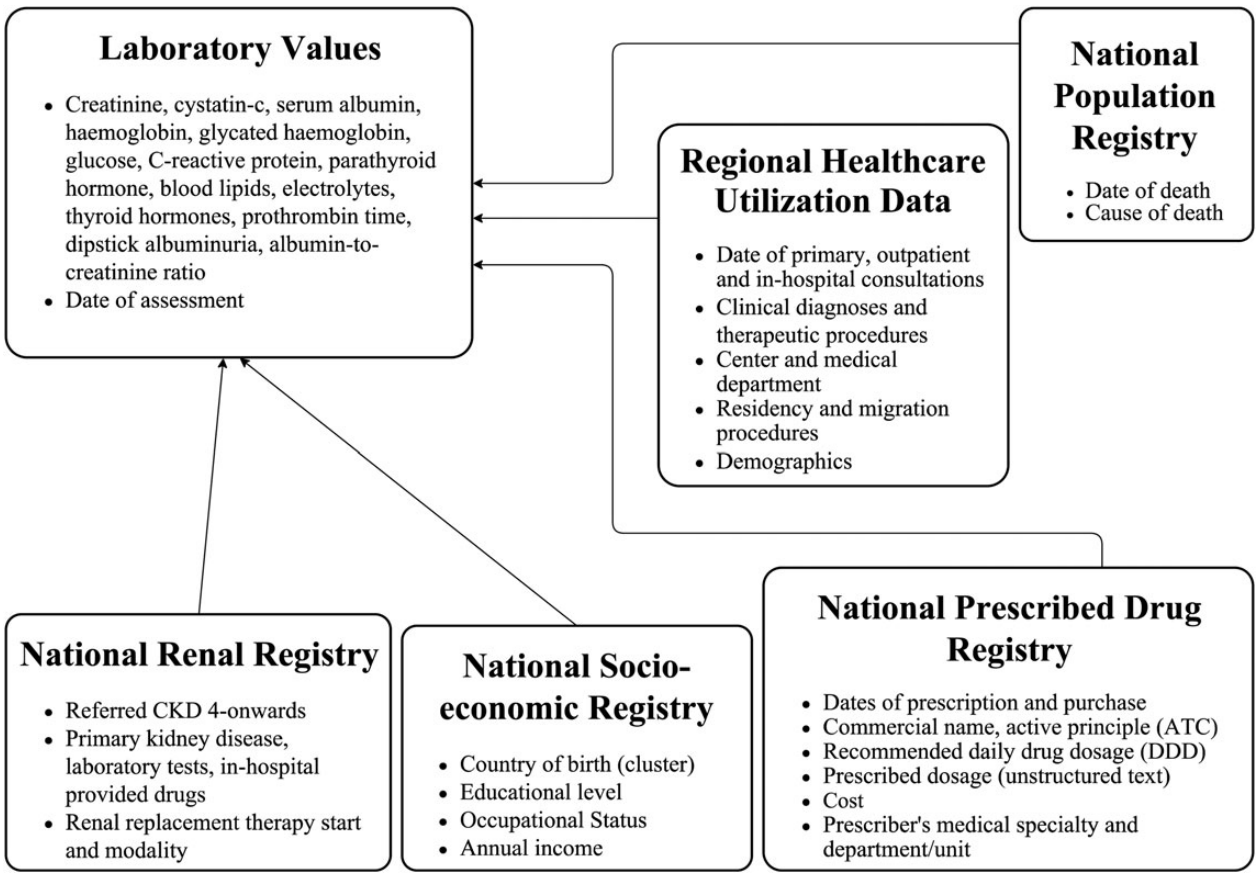

Fig. 1. Data sources and information linked to the Stockholm CREAtinine Measurements (SCREAM) project.

The Swedish Prescribed Drug Registry, a nationwide registry instituted in 2005 and collecting information on all prescription drugs dispensed at Swedish pharmacies. This register had complete coverage (>99.7%) of all dispensed drugs. It also contains information on the practice (primary health care centre or clinic) and profession/medical specialty of the prescriber. Drugs were reported by their generic names as well as active principle ATC codes, together with the number of defined daily doses dispensed and the costs (both reimbursed expenditure and patient co-payment). Information on actual prescribed dosage was available as unstructured text. This register did not contain information on over-the-counter pharmaceuticals, nor ambulatory or in-hospital care drugs given at hospitals. Neither did it completely cover drugs used at nursing homes or vaccines [29]. Drug dispensing data were requested for each individual since 2006 and up to 31 December 2012.

The Swedish Population Registry recorded, on a monthly basis, information on vital status for each Swedish citizen with virtually no loss to follow-up. In case of death, the reported cause of death was recorded as well. Vital status information was requested for each individual from inclusion in SCREAM up to 31 December 2012.

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA by Swedish acronym) (http://www.scb.se/en_/Services/Guidance-for-researchers-and-universities/SCB-Data/Longitudinal-integration-database-for-health-insurance-and-labour-market-studies-LISA-by-Swedish-acronym/.eng) combined information from several sociodemographic population registers. Variables included country of birth, educational level, occupational status and income level. All Swedish citizens older than 16 years residing in Sweden as of 31 December were registered and the information was updated on a yearly basis.

The Swedish Renal Registry [30] included Swedish patients referred to a nephrologist and diagnosed with CKD. Inclusion was encouraged to all hospitals from CKD Stage 3b and considered mandatory from the first diagnosis of CKD Stage 4. Information from patient visits during the non-dialysis phase and until renal replacement therapy start (first chronic dialysis or renal transplantation) was collected, with additional data collection on primary kidney disease, laboratory tests (such as uric acid) and in-hospital provided drugs to treat kidney diseases. Upon start of dialysis, a patient visit was recorded annually detailing in addition dialysis modality and specifications (dialysis dose, fistula/graft, etc.). Information from this registry was requested since its establishment in 1999 up to 31 December 2012.

After all requested data were linked, patient identification was substituted by a random identifier, safeguarding patient privacy and confidentiality. The key to decipher the identifiers was kept at the National Board of Health and Welfare for amendments, follow-up expansions and/or new linkages to the extraction. Only then, the complete SCREAM project, including more than 200 datasets, was sent to the responsible investigators. Data was stored at encrypted and secured servers at SLL. Data were analysed according to our university rules and ethical standards and the project was reviewed and approved by the Ethical Committee of Stockholm.

Practical implementation plan of research findings

In parallel with building the SCREAM dataset SLL was developing a clinical decision support system for the prescription of pharmaceutical drugs to patients with reduced kidney function (NjuRen© [31]). NjuRen© was an electronic application integrated to the health-records that assists prescribers by automatically estimating kidney function using the latest available creatinine assessment, gender and age. By combining this information with the information on prescribed drugs the prescriber was informed, when applicable, of kidney–drug contraindications, nephrotoxicity, and the need for dose adjustment and/or safer drug alternatives for the patient. NjuRen© started to be implemented in all healthcare centres of the region in 2014. This current SCREAM extraction will serve to document IDU rates and its clinical consequences in the region of Stockholm. SCREAM will identify which drugs, medical specialties and population segments are susceptible to IDU, and this knowledge will be used to develop educational/corrective programs. During 2017, a second laboratory extraction will take place (SCREAM-2), adding laboratory assessments and clinical practices for the period 2012–16. This will serve to assess the effectiveness of NjuRen© implementation by comparing the expected change in inappropriate drug utilization rates among NjuRen© participating centres. This analysis of program effectiveness will motivate the expansion of NjuRen© to other regions in Sweden. Additionally, the second data extraction will allow capturing recent drugs and clinical practice changes.

Assessment of SCREAM's regional coverage and representativeness

Methodological considerations

The coverage of SCREAM was assessed by comparing the number of SCREAM individuals with the complete Stockholm population. For that purpose, a comparable extraction of general population statistics was performed from VAL. This included adult (≥18 years old) citizens of the Stockholm region during 2006–11 ($n = 1\,706\,259$ individuals). Citizenship was ascertained by being censored in any of the 26 municipalities of the region at least once during the study period. For comparative purposes, age was defined as of 1 January 2006 in both materials. Summary statistics for age and sex strata as well as number of citizens per municipality were provided and compared with SCREAM. Since assessment of creatinine was particularly indicated in specific comorbidities, we ascertained the coverage of SCREAM in cardiovascular disease and diabetes mellitus patients. For this, we classified individuals according to the presence of at least one relevant ICD-10 code during the period coming from a secondary or tertiary healthcare consultation. Cardiovascular disease was defined with the following four Charlson domains [26, 27]: acute myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular disease; diabetes mellitus was defined with the two Charlson domains of diabetes. Finally, being this an extraction of individuals seeking healthcare, we expected to have a sicker population with an over-representation of occurring deaths. To that end, we compared the number of deaths per calendar year in SCREAM with those recorded for the general population.

Results

SCREAM identified a total of 1 344 197 individuals with at least one serum creatinine assessed during the study period. For this analysis, we excluded individuals not residing in the Stockholm County ($n = 85\,667$) and those younger than 18 years old ($n = 140\,023$). Therefore, the analysis of SCREAM coverage and representativeness was based on 1 118 507 Stockholm citizens in the adult age range. Roughly, one-third of the Stockholm population underwent at least one creatinine assessment

annually (25, 34, 35, 36, 34 and 33% across the years 2006–11, respectively). Since different individuals were assessed every year, the number of unique individuals with creatinine assessed during the whole period 2006–11 corresponded to 66% of the Stockholm population. The coverage was equally distributed throughout the 26 municipalities of the region, ranging from 62% coverage in Stockholm city, to 72% in Norrtälje (Figure 2).

Coverage by age and sex strata is depicted in Figure 3A. The coverage was slightly higher for women than for men in the age range of 18–64 years, thereafter becoming equal between the sexes. Because creatinine assessment is more frequently assessed in older ages, SCREAM's coverage increased with age; SCREAM captured ~50% of all individuals in the range of 18–44 years old, >75% of individuals aged 45–64 years and >90% of all

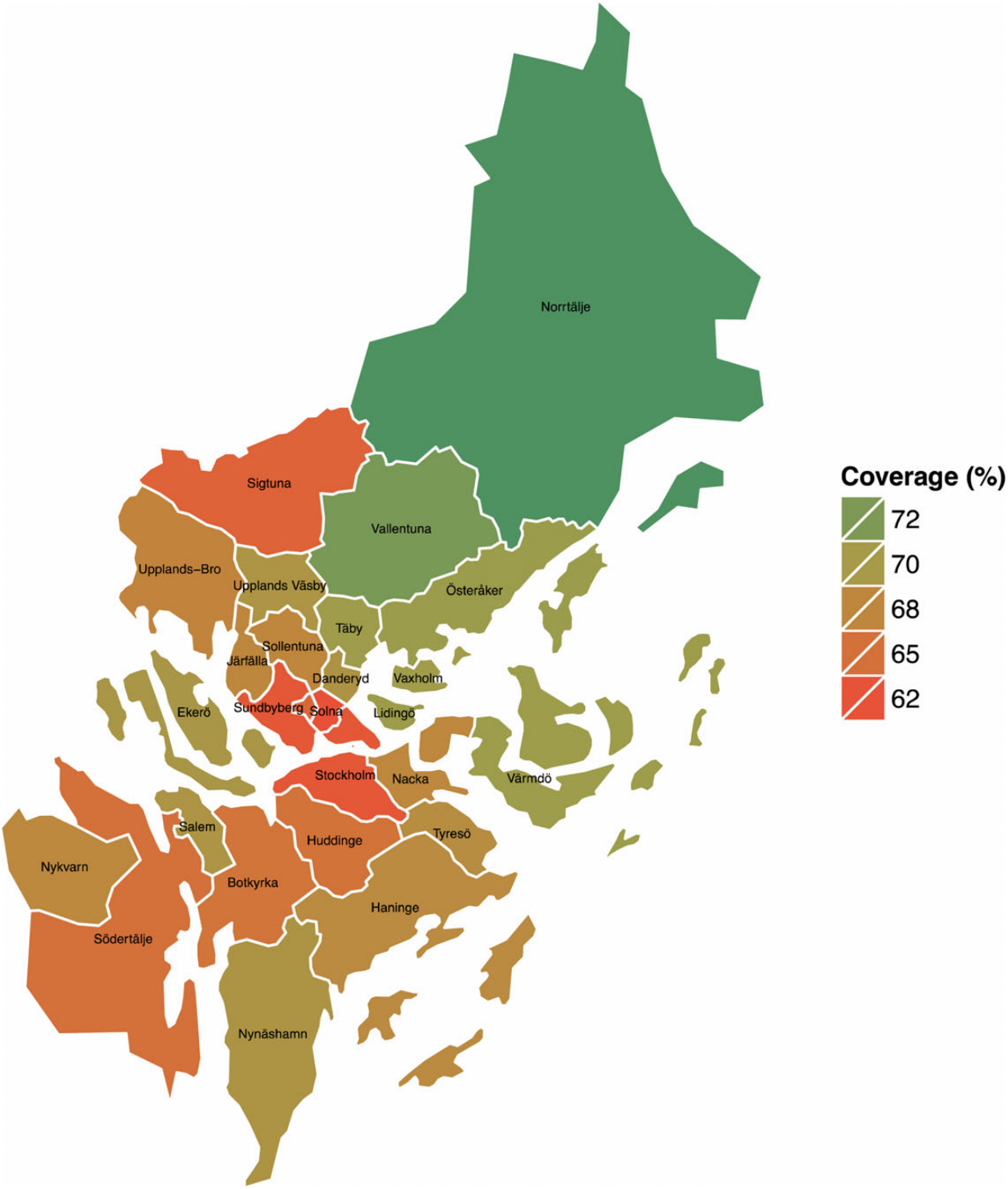

Fig. 2. Proportion of the adult Stockholm population included in SCREAM; geographical coverage by municipality.

individuals aged ≥65 years old. The distribution of age and sex in SCREAM was very similar to that of the Stockholm population (Figure 3B).

As many as 98% (121 785 versus 124 092) of all individuals with a cardiovascular disease (CVD)-related diagnosis are captured by SCREAM. Likewise, 97% (78 125 versus 80 188) of individuals with a diabetes code were included. The proportion of CVD and diabetes cases in SCREAM and in the general population was rather similar (Figure 4), with an expected slight overrepresentation of both diseases in SCREAM. During 2006–11, 91 353 deaths occurred

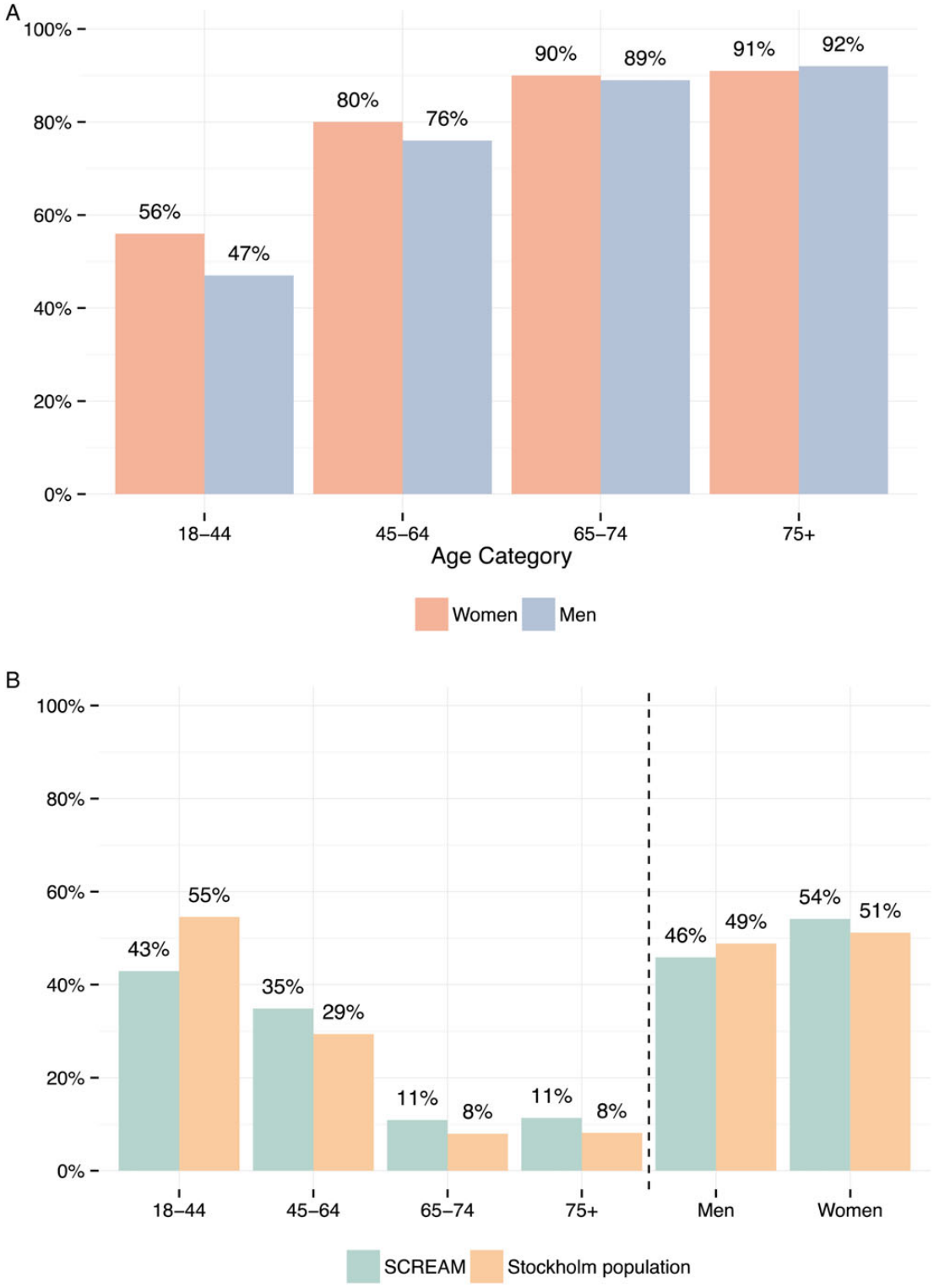

Fig. 3. Proportion of the Stockholm population included in SCREAM, stratified by age and sex (**A**); age and sex distribution in SCREAM and in the complete Stockholm population (**B**).

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Fig. 4. Proportion of individuals with CVD (**A**) or diabetes mellitus (**B**) ascertained by ICD-10 codes from secondary or tertiary healthcare consultations during 2006–11 in the Stockholm population and in SCREAM.

in the general population. According to our 66% population coverage, ~61 000 deaths were to be anticipated in SCREAM. In all, 89% ($n = 81\,270$) of deaths were captured in SCREAM, being the expected difference attributed to the selection criterion of individuals in need of healthcare.

Discussion

The SCREAM cohort represents to date the largest patient material to estimate the burden and implications of CKD in Sweden, and probably one of the most comprehensive healthcare

extractions to assess the implications of kidney function in healthcare management. The coverage and representativeness of the region of Stockholm is high and in accordance with both the commonness of creatinine assessment in healthcare, and medical indications for creatinine tests. The richness of information retrieved, including both laboratory values and complete healthcare utilization data is unique and can be used for the study of other chronic medical conditions beyond CKD. Strengths of SCREAM are the personal identity number unique to all Swedish citizens and the possibility to continuously enrich data, increasing completeness and minimizing loss to follow-up. Since healthcare in Sweden is tax-financed (to a large extent including also the cost of medications), we believe that confounding related to socioeconomic status, affecting the probability of adhering to the treatment, is lower than in other countries. However, there are important limitations as well; first, we use the existence of creatinine assessment to define our study cohort, which although reflects standard clinical practices, limits our study to subjects who have sought medical care and had a creatinine test undertaken (selection bias). The indications for creatinine measurement in SCREAM are unknown. However, judging by the high representativeness of the Stockholm population, especially among the older age stratum, this is unlikely to invalidate our findings. Finally, we lack certain clinical variables of importance such as body mass index, blood pressure and lifestyle factors (smoking habits, exercise), which may confound our conclusions. Nevertheless, some of them can be indirectly captured by specific ascertainment of comorbidities and medications.

Other healthcare extractions have been performed in the past, but representativeness has seldom been estimated in those. SCREAM is a cohort by indication of assessment, and from this analysis, it can be concluded that SCREAM findings can be well generalized to the elderly individuals (≥65 years old) of our region (>90% coverage). Likely, SCREAM can be fairly generalized to individuals in the age range 45–64 years (>75% coverage). The lowest representativeness is found for younger ages (<45 years), which may not have the same indications for creatinine testing. Still, SCREAM captures ~50% of individuals in this category. This prompts the need to stratify future study results across these age ranges and ponder both patient selection and conclusions having coverage and testing by indication in mind. The coverage of diseases with indications for creatinine testing is also virtually complete (>97%), that is, all patients with diabetes or CVD during the observation period have had at least one creatinine test. Thus, SCREAM has an excellent quality to study cardio-renal and diabeto-renal complications, treatments and management. In an ulterior sphere, this analysis shows that creatinine is already measured in a larger proportion of the community. Although screening programs are necessary, improved patient care can be achieved by interpreting the information that we already have and integrated in the medical decision process.

Community approaches to pharmacy-IDU are scarce, with previous evidence focussing on restricted population segments such as the elderly or restricted to in-hospital admissions and single-centre experiences [13, 15, 19–21]. It has been demonstrated that clinical decision support systems to guide medication dosing improved the appropriateness of dosage by 13% and appropriateness of frequency by 24% in the USA [22]. In a cross-sectional trial from Belgium, the implementation of a computer-assisted medical support system in the intensive care unit-setting, reduced by 3-fold the rate of medication prescription errors in patients with renal insufficiency [23]. We are positive that our efforts to identify IDU coupled with the implementation of NjuRen© in our region may improve this.

To conclude, SCREAM is a region-representative repository of laboratory data linked to regional and national registers that can be used for health services and health policy research in which kidney function has or may have an impact. Research collaborations are certainly welcome, including as well the possibility to link SCREAM data to other Swedish registers via each citizen's personal identification number.

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Conflict of interest statement

None declared.

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