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Long-term evolution of renal function in patients with type 2 diabetes mellitus: a registry-based retrospective cohort study

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Abstract

Aim: To picture the 10-year evolution of renal function in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) and to describe the risk factors for severe decline (SD)

Method: In a primary care based morbidity registration network we selected all patients aged 40 years or older with T2DM and at least two creatinine measurements in two different years with an interval of at least 3 months. Based on the last available value of eGFR calculated by the MDRD equation, patients were divided into grades of CKD. SD (decline of > 4 ml/min/year) and "certain drop" (year-to-year decline > 10 ml/min) were determined in patients with CKD. Determinants of severe decline and certain drop were investigated with logistic regression and longitudinal logistic regression analysis, respectively.

Results: 4041 patients -1980 female - were included. Mean age was 71 years, mean diabetes duration 7.7 years; 1514 (38%) suffered from CKD, 231 (15%) presented with severe decline, 18% of the patients with CKD presented with 2 or more certain drops. Younger age, male gender, mean HbA1c and a higher number of certain drops were significantly associated with the presence of severe decline ($p<0.05$) ; statins and higher diastolic blood pressure were significantly associated with the absence of severe decline ($p<0.001$). ACE inhibitors, other antihypertensive drugs and anti-diabetic drugs including insulin therapy were specific determinants of certain drop.

Conclusions: CKD is highly prevalent in T2DM patients; a minority of patients evolve into severe decline that is associated with younger age, male gender and manageable factors like blood pressure, blood glucose, associated drugs prescriptions and statin therapy.

Abbreviations:

ATC: Anatomical Therapeutic Chemical Classification System
BMI: Body Mass Index
CKD: chronic kidney disease
CVD: cardiovascular disease
ESRD: end-stage renal disease
GP: general practice
GPs: general practitioners
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICPC-2: International Classification of Primary Care, second edition
MDRD: Modification of Diet in Renal Disease
NSAID: non steroidal anti-inflammatory drugs
NCD: number of certain drops
OAD: oral anti-diabetic drugs
OR: odds ratio
OS: overall slope
T2DM: type 2 diabetes mellitus
UK: United Kingdom
WHO: World Health Organisation

What is known

Chronic kidney disease is highly prevalent in patients with type 2 diabetes mellitus. Other risk factors are high blood pressure, obesity, older age, high cholesterol and a family history of chronic kidney disease. Poorly controlled diabetes increases the risk that chronic kidney disease will eventually lead to kidney failure.

Little is known about the long-term evolution of kidney function in patients with diabetes and CKD. Knowledge is also limited about supplementary risk factors of kidney deterioration in patients with T2DM and CKD.

What this study contributes

- Eighty-five percent of all patients with diabetes and CKD keep a stable kidney function for many years.
- Especially younger, male patients are at risk for severe decline of kidney function and evolution to renal failure.
- Long-term severe decline is also associated with poor blood glucose control and the presence of periods of sudden, rapid decline, itself associated with the prescription of ACE inhibitors, other antihypertensive agents and anti-diabetic drugs, including insulin therapy.
- Statin therapy and higher diastolic blood pressure were associated with lower odds of severe decline.

Strengths and weaknesses

Strengths:

- The study population: a large primary care population that is representative of the population in Flanders with automatic inclusion of laboratory tests performed in primary care and a large proportion of the tests performed in hospitals.
- The database also contains all introduced diagnoses and most of the relevant clinical parameters.
- Strengths inherent to a retrospective design with long-term follow-up of the clinical and biological parameters. At least 2 eGFR measurements were available for all patients,
- Data analyses with longitudinal models incorporating between- and within-subject analyses with inclusion of timely changes in diagnoses and drug prescriptions.

Weaknesses:

- Lack of mortality data, data on renal replacement therapy and insufficient data on proteinuria/albuminuria and Body Mass Index (BMI).
- Weaknesses inherent to a Retrospective design and registry data: possible healthy survivor bias, no information about missing data and loss to follow-up

- **Introduction**

The prevalence of both type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) is rapidly growing, with an expected doubling of the number of people with diabetes worldwide within the next 20 years (1). Patients with T2DM present a 25-40% lifetime risk of developing CKD (2). Patients with comorbid T2DM and CKD are at major risk for cardiovascular disease (CVD) and premature mortality (3). Thus, management of Type 2 Diabetes and CKD, as well as risk factor control seem to be a daunting challenge both for individual patients and for public health (4-6). Besides T2DM, major risk factors for CKD include cardiovascular disease, hypertension and obesity (4;7;8).

Despite a large prevalence of CKD, only a minority of those patients develop end stage renal disease (ESRD) (3). Besides kidney function at a given moment, the speed of decline of kidney function also plays a major role in the development of ESRD (9). Faster progression of CKD is also associated with higher mortality (10). Little is known about the risk factors in patients with CKD of rapid progression and serious complications (11). In addition, the use of eGFR alone, especially in elderly people, may lead to false positive diagnoses of CKD because the decreased eGFR could just represent an age-related functional decline.

T2DM is known to be by far the leading cause of ESRD in developed countries (12). Again, it is not known how many and what kind of patients with T2DM will develop ESRD. Very few studies have reported on the long-term evolution of renal function in patients with diabetes and determinants of deterioration of kidney function. Therefore, based on the data of a primary care registry, we wanted to investigate the severity of CKD in patients with T2DM. More specifically, we retrospectively analysed how renal function evolved over a period of 11 years - between 2000 and 2010 - in patients with T2DM and what risk factors were associated with deterioration of renal function.

Methodology

Design and data collection

We performed a retrospective cohort study on patients with type 2 diabetes using a general practicebased morbidity registration network (Intego). Intego started to collect data in 1994 but in the present study, data were used from 2000 until 2010. Ninety-seven GPs, all using the medical software program Medidoc®, collaborate in the Intego project. These 97 GPs work in 55 practices evenly spread over Flanders, Belgium. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The Intego GPs prospectively and routinely registered all new diagnoses together with new drug prescriptions, as well as laboratory test results and some background information (including gender and year of birth), using computer generated keywords internally linked to codes.

Using specially framed extraction software, new data were coded and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus automatically linked to the ICPC-2 (International Classification of Primary Care) and ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision). Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.

The inclusion criterion for the present study was the presence of the diagnosis of "type 2 diabetes" in the patient' file (ICPC-code T90). Exclusion criteria were an age below 40 years at the reported date of diagnosis of diabetes. Included patients also should have at least two creatinine (MDRD) measurements in two different calendar years, with a measurement interval of at least 3 months.

The variables of interest considered in this study included the age (year of birth), age at diagnosis of diabetes, creatinine, HbA1c, systolic and diastolic blood pressure, LDL cholesterol, gender and hypoglycaemic treatment group (diet, oral drugs only, combined oral antidiabetics (OAD) and insulin, insulin only), use of ACE inhibition, other antihypertensive medication, platelet inhibition, lipid lowering drugs, NSAID and the presence of different pathologies, such as cardiovascular disease (CVD) – defined as a history of stroke, ischaemic cardiac disease or peripheral arterial disease -, CKD, combined neuropathy and retinopathy, gout, anaemia, anxiety-depressive disorders, osteoporosis, dementia and malignancies.

For LDL-cholesterol and HbA1c, we withheld the last value of each year for longitudinal analysis. Both parameters are stable over time unless some intervention is carried out. Moreover, HbA1c represents a "weighted" average of blood glucose levels during the preceding 120 days with glucose levels in the preceding 30 days contributing about 50% to the final result (13). As such, HbA1c only changes progressively over three months when treatment changes. Taking the yearly average would

include the danger of smoothing away hypoglycaemic treatment effects.

Regarding creatinine we took the average value of the last two measurements of each year in order to account for the important within-subject variability of this variable.

Finally, blood pressure is very prone to within-subject variability and to the "white coat hypertension" phenomenon, i.e. systematically increased values for all measurements taken by a professional and to increased values of the first measurement by a professional, improving after repetition (14). Therefore, we took into account the last three blood pressure measurements of each year and used the average of the lowest two values of these three measurements.

The eGFR was calculated with the Modification of Diet in Renal Disease (MDRD) formula: glomerular filtration rate (GFR) (mL/min/1.73 m2) = 186 × (Scr)−1.154 × (age)−0.203 × 0.742 (if female). We defined diagnosed CKD in patients if they presented two MDRD values <60 ml/min with an interval of at least three months. We used the classification system of the American Kidney Foundation to classify the patients: eGFR between 45 and 60 mL/min/1.73m2 = Grade 3A, eGFR between 30 and 45 mL/min/1.732 = Grade 3B, eGFR between 15 and 30 mL/min/1.73m2 = Grade 4 and eGFR <15 mL/min/1.73 m2 = Grade 5. In this definition, patients with CKD stages 1 and 2 were excluded from analysis.

We calculated the overall slope (OS) of eGFR evolution as the difference between the last MDRD value and the first MDRD value divided by the number of interval years. Based on previous studies, patients were divided into three groups: no decline (OS≥0), mild to moderate decline(-4≤OS<0) and severe decline (OS<-4) ((10). We also calculated the year-on-year difference in MDRD in the longitudinal dataset and defined "certain drop" as a decrease in year-on-year MDRD >10ml. For each patient we counted the number of certain drops during the study period and defined it as the number of certain drops (NCD). We also divided the patients according to their age, with a first age group between 40 and 65 years, a second group between 66 and 80 years and a third group aged over 80 years.

Neither microalbuminuria nor proteinuria were withheld in the analysis because of data collection issues (too few collections; no control on validity of measurement).

Statistical analysis

All analyses were performed with STATA 12.1 (StataCorp, Texas). Continuous parameters are shown as Mean±SD, binomial and multinomial parameters as percentages, and 95% CI. Significance tests were performed by t-test for continuous and χ^2 for dichotomous parameters. We built 3 regression models. The first model was a logistic model that analyzed the determinants of grade 5 CKD, used as a proxy for ESRD. The second model, a logistic regression model, aimed to examine the determinants of severe decline in patients with and without CKD. The last model, a longitudinal logistic model with random effects, examined the determinants of certain drop in patients with and without CKD.

Model building was performed in a concise manner. In the longitudinal logistic model, the individual patient was defined as panel variable. Each year was considered as 1 time unit with the year 2000 set as 0. All time evolving parameters (new diagnoses, new drugs prescriptions) were disaggregated according to the year of introduction in the database (level 1). The only exceptions were "diabetes" and "diabetes duration", presented as level-2 parameters. In the logistic regression models, variables were aggregated. We used the overall mean values of HbA1c, SBP, DBP and LDL values as model variables. Drug prescriptions were accepted if they had been prescribed for three years or more. Only the diabetes treatment was based on the latest available data (year 2010). Diagnoses were accepted if they had if they have been included in the register, whatever the year.

In a first step, determinants were selected by binary models if $p<0.1$. Secondly, all determinants were put in 1 model and manually eliminated by stepwise backward regression. Only those determinants with $p<0.05$ were withheld in the models, except for age, gender and CKD (for which all models were adjusted).

Since all analyses are likelihood based, valid inferences can still be obtained under the assumption of random missingness, i.e., the fact that a variable is missing for a patient is unrelated to the outcome that would have been measured for that patient.

The Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (no ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079).

Results

The cohort included 4041 patients with T2DM of whom 1514 (38%) presented with CKD in 2010 and 988 (24%) with CKD grade 3a or higher. As shown in table 1, they significantly differ from patients without CKD for several parameters like age, gender, diabetes duration, history of CVD and non diabetes related co-morbidity. Of those patients with CKD, 526 (35%) presented with grade 1 or 2, 534 (35%) with grade 3a, 311 (21%) with grade 3b, 110 (7%) with grade 4 and 33 (2%) with grade 5. As shown in figure 1, most patients with CKD remain stable for a long period. Indeed, 425 patients with CKD (28%) present no decline, 857 (56%) patients present moderate decline and 232 patients (15%) present severe decline. It is interesting to note that, in patients without CKD in 2010, only 7% present with severe decline.

CKD, including moderate or severe grade CKD were more prevalent in elderly people (table 2, p= 0.004). However, the proportion of patients with a severe decline tended to decrease with increasing age (40-65 yrs:25% ; [19-32]- 66-80 yrs: 16%;[13-18] - >80 yrs: 11%;[9-14]). This decrease was not observed in people without CKD (40-65 yrs: 7.8%;[6,3-9,] – 65-80 yrs:7,1%;[0,5,6-8,6] - >80yrs 8.2%[5,3-11,9].

At least 1 certain drop was present in 59% (CI 95% 56-61) of patients with CKD and in 49% (CI95% 44-51) of patients without CKD, with 5 as a maximum number of certain drops. In patients with severe decline, prevalence of at least 1 certain drop was considerably higher than in patients without severe decline: 86% (CI 95% 81-90) versus 54% (CI 95% 51-57) in patients with CKD and 77% (CI 95% 70-83) versus 46% (CI 95% 44-48) in patients without CKD.

The first logistic regression model only showed 2 determinants for CKD grade 5: the baseline value of MDRD (OR= 0.95, CI 95% [0.98-0.99]) and presence of severe decline (OR= 27.71, CI 95% [3.62-212.16]).

The second logistic regression model showed a significant interaction between age group, gender and the number of certain drops (NCD) on the one hand, and CKD on significant decline on the other hand. Thus, different logistic models were built for patients with and without CKD (table 3). In patients with CKD, severe decline is associated with younger age, male gender (OR 1.73 [1.25-2.38]), mean HbA1c value (OR 1.33, [1.13-1.56]) and the number of certain drops (OR 2.31 [1.96-2.72]. Statin use [OR 0.69 [0.50-0.96] and DBP (OR 0.97 [0.94-1.00] are associated with lower odds of severe decline. In patients without CKD, age, gender and DBP do not have a significant effect on severe decline.

The longitudinal logistic model showed a significant interaction between time, age group, gender, anti-diabetic treatment, statin treatment and several co-morbidities (anaemia, osteoporosis, malignancy, anxious depression and gout) with CKD on the appearance of certain drop. Again, we built separate models for patients with and without CKD (table 4). Appearance of certain drop in patients with CKD was associated with male gender (OR 1.20 [1.05-1.36]), oral anti-diabetic treatment (OR 1.32 [1.14-1.52]), insulin treatment (OR 1.55 [1.29-1.86]), ACE inhibition (OR 1.31 [1.14-1.50]) and other antihypertensive treatment (OR 1.23 [1.07-1.42]), while age>80 (OR 0.82 [0.72-0.95]) and statin use (OR 0.86 [0.75-0.99]) were associated with lower odds (table 4). Associations were partly different in patients without CKD: younger age (40-65 years) was associated with lower odds, gender had no significant association, and statin treatment as well as several co-morbidities were associated with higher odds of certain drop.

Discussion

The results of our retrospective cohort study confirm previous findings about the high prevalence of CKD in patients with Type 2 Diabetes (15-17). However, although the fact that T2DM is a known risk factor for the development of CKD, this study also shows the presence of a great variability between T2DM patients regarding the decline in kidney function. Patients with CKD evolve in a different manner than patients without CKD and more people with CKD present with severe decline. Even in people with established CKD, only a minority (15%) of the patients present

with severe decline. Interestingly in our study, severe decline and the 'baseline value' of MDRD are the only independent risk factors that are associated with progression to Grade 5 CKD, used as a proxy for end stage renal disease. Most patients with CKD - even with grade 3a, 3b or 4 - remain stable for many years. As such, the results of our study support the proposition of Al Aly and Cepeda that CKD should be defined in a dynamic way, taking into account both the CKD grade and the decline of kidney function (18). More specifically, age and gender interact with CKD in their effect on severe decline: in patients with CKD, but not in patients without CKD, severe decline is more prevalent in younger patients and in males. This observation may indicate that the current definition of CKD misclassifies some people, especially elderly and female persons, as patients suffering from chronic kidney disease.

In patients with CKD, severe decline is also associated with (potentially) manageable factors. Higher levels of HbA1c and a higher number of certain dropcertain drops are associated with higher odds of severe decline, while higher levels of Diastolic Blood Pressure and statin therapy are associated with lower odds of severe decline. certain drops can be interpreted as moments or periods of rapid decline alternating with longer periods of stable kidney function. Some previous studies already suggested an association between ESRD and periods of rapid decline. (19;20) Certain drop may also be related to the findings of a meta-analysis that revealed that acute kidney injury is a determinant of CKD and ESRD (21). Certain drop" and acute kidney injury may be two gradations of rapid collapse in kidney function responsible for an unfavourable evolution of kidney function in patients with CKD. However, patients without CKD are also prone to certain drop. Apparently, some people recover from brutal decline while others do not. From a clinical point of view, it would be interesting to quantify the impact of some determinants on severe decline and certain drop of kidney function, especially those which are manageable, such as nephrotoxic agents, infections, poor cardiovascular conditions or poor glucose control. Several drugs like ACE inhibitors, other antihypertensive drugs and anti-diabetic drugs including insulin therapy, are associated with higher odds of certain drop, while statins are associated with lower odds. In the framework of our study, it is not possible to interpret the nature of this relationship in causal terms. For instance, it is known that the initiation of ACE inhibitors can cause decline in kidney function in some people, but in our study, kidney function could eventually also deteriorate in some people despite ACE inhibition. The association between co-morbidity (anaemia, osteoporosis, anxious depression and malignancy) and certain drop in patients without CKD, but not in patients with CKD, is another interesting result worthwhile exploring.

Other determinants, such as insufficient glycaemic control (higher HbA1c levels), may have a slowly damaging effect on the kidney function, while statins are associated with a protective effect. Curiously, a higher DBP is associated with lower odds of severe decline in patients with CKD, but not in patients without CKD. Literature is contradictory regarding the impact of DBP on kidney function decline. Some studies describe a negative association between higher DBP and kidney decline (22)

while others mention a positive association (23). Our finding may be related to the conclusion that increased rates of pulse pressure are related to progression of renal impairment (24;25), even if in our study, pulse pressure was not an independent risk factor.

Only few studies have reported about kidney function decline in patients with T2DM. Zoppini (26) et al. reported a significant effect on kidney function decline of hypertension, increased HbA1c, longer diabetes duration, obesity, insulin treatment, microalbuminuria and macroalbuminuria. Cummings et al. found that age, mean systolic blood pressure, initial HbA1c, initial eGFR, and the number of HbA1c values were significant predictors of change in eGFR (27). Lin et al. did not find any association between blood lipids and kidney function decline (28). These outcomes are only partially in line with our results.

Strengths and weaknesses

The major strength of this study is the study population being a large primary care population that is representative of the population in Flanders (29). The database automatically incorporates all data of laboratory tests performed in primary care and a large proportion of the tests performed in hospitals. The database also contains all introduced diagnoses and most of the relevant clinical parameters. It allows a follow up the long-term evolution of clinical and biological parameters. At least 2 eGFR measurements were available for all patients, and longitudinal models were applied to analyze the data, incorporating between- and within-subject analyses with inclusion of timely changes in diagnoses and drug prescriptions.

The study also has some weaknesses. First, we had no mortality data, nor data on renal replacement therapy. Secondly, although it is a well-known risk factor for the progression of CKD (30;31), we had no data on proteinuria/albuminuria because these were not frequently measured. We also did not have enough data on the Body Mass Index (BMI) to incorporate this variable in multivariate models. Using these data would have induced an important selection bias. However, laboratory tests were performed for clinical reasons. As such, the results give an idea of the "normal" working method of the GP: the lack of data on albuminuria and BMI gives an indication about a gap in the follow-up of patients with diabetes in primary care in Flanders.

In conclusion, despite the large prevalence of CKD in patients with T2DM, only a minority present with rapid, severe decline and evolve into ESRD. Kidney function in patients respectively with and without CKD evolves differently, with age and gender acting as interaction factors. In patients with CKD, but not in patients without CKD, kidney function decline tends to be more aggressive in younger and in male patients. Conversely, kidney function decline in elderly people, even if CKD is present, is not necessarily an aggressive, pathologic process. Our study also revealed the association of severe decline and/or certain drop with several potentially ‘manageable’ determinants like HBa1C,

diastolic blood pressure, statin therapy, ACE inhibition, other antihypertensive agents and anti-diabetic drugs including insulin therapy. However, because of its retrospective character, this study is able to formulate hypotheses, but further prospective observational and experimental research is needed to clarify the nature of those associations.

Competing interests: "All authors have completed the ICMJE uniform disclosure form at twww.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

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All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: no additional data available

Table 1. Characteristics of the diabetes population in 2010 for all patients, stratified according to the presence or not of CKD.

	All patients			No CKD (62%)			CKD (38%)			
Variable	Obs	Mean/%	SD	Obs	Mean/%	SD	Obs	Mean/%	SD	p
male	4041	51%		2527	59%		1514	38%		<0.0001
age	4041	71	11	2527	67	10	1514	77	9	<0.0001
diabetes duration	4041	7.7	6.3	2527	6.6	5.6	1514	9.6	6.9	<0.0001
HbA1c (%)	3128	6.9	1.0	1930	6.9	1,1	1198	6.9	1.0	0.056
HbA1c (mmol/mol)	3128	52	13	1930	52	13	1198	52	13	0.056
MDRD	3260	72	23	1991	85	17	1269	52	17	NA
severe decline	4041	10.4%		2527	7.5%		1514	15.3%		<0.001
% with ≥ 2 certain drop	4041	18.3%		2527	15.8%		1514	22.5%		<0.001
LDL cholesterol	2868	98	33	1823	100	33	1045	95	33	<0.001
SBP	2887	136	14	1848	135	14	1039	136	15	0.224
DBP	2887	79	8	1848	80	8	1039	77	8	<0.001
CVD	4041	29.1%		2527	22%		1514	40%		<0.001
smoking	1254	14.7%		816	17%		438	10%		0.001
diabetes treatment	4041			2527			1514			
lifestyle only	1510	37.3%		896	35%		614	41%		
OAD	2013	49.8%		1385	55%		628	41%		<0.0001
insulin	518	12.8%		246	10%		272	18%		<0.0001
antihypertensive	4041	54.5%		2527	51%		1514	60%		<0.0001
ACE inhibitors	4041	44.1%		2527	42%		1514	47%		0.007
platelet inhibition	4041	39.6%		2527	39%		1514	41%		0.145
lipid lowering	4041	48.1%		2527	49%		1514	46%		0.046
anaemia	3927	3.5%		2472	2.5%		1455	5.2%		<0.001
osteoporosis	3927	4.2%		2472	2.75%		1455	6.75%		<0.001
psychological distress	3927	11.3%		2472	10.5%		1455	12.7%		0.042
dementia	3927	1.3%		2472	1.1%		1455	1.7%		0.107
malignancy	3927	7.1%		2472	5.1%		1455	10.5%		<0.001
gout	3927	8.0%		2472	6.9%		1455	9.9%		0.001

Table 2. Comparison of kidney-related parameters in patients with CKD, according to the age group.

Age in 2010	40-65 years*		66-80 years		> 80 years	
Variable	N=189/1345 (14%)		N= 765/1842 (41%)		N= 560/854 (66%)	
% with grade 3a -> 5	61%	[54-68]	64%	[60-67]	69%	[65-73]
% with CKD & severe decline	25%	[19-32]	16%	[13-18]	11%	[9-14]
% with CKD & two or more certain drops	27%	[21-34]	26%	[23-29]	16%	[13-20]
Mean MDRD in 2010	56	[54-58]	53	[51-54]	50	[48-51]
Mean CKD duration (yrs)	5.8	[5.3-6.5]	7.8	[7.4-8.1]	9.2	[8.9-9.7]

For dichotomous variables: % and exact (binomial) confidence interval of 95%

For continuous variables: mean value and confidence interval of 95%

Table 3. Logistic regression model analysing the odds of severe decline and its determinants in patients with (N= 1469) and without CKD (N=2385).

	Presence of CKD (N=1469)			**Absence of CKD (N=2385)**		
	Odds Ratio	[95% Conf.	Interval]	Odds Ratio	[95% Conf.	Interval]
age 66-80*	0.55	0.36	0.85	0.85	0.61	1.18
age>80*	0.41	0.25	0.67	1.02	0.63	1.66
male	1.73	1.25	2.38	1.01	0.74	1.38
HbA1c (%)	1.33	1.13	1.56	1.20	1.05	1.37
Statin****	0.69	0.50	0.96	0.68	0.48	0.95
NCD	2.31	1.96	2.72	1.69	1.43	1.98
DBP (mm Hg)	0.97	0.94	1.00	//	//	//

* reference group age 40-65 years

***Drugs were included in patients' treatment if they had been prescribed for three years or more.

Table 4. Longitudinal logistic regression model with random effect analysing the odds of certain drop and its determinants in patients with CKD (N=1514) and without CKD (N= 3452).

	Patients with CKD (N=1514)			Patients without CKD (N=3452)		
	OR	[95% Conf.	Interval]	OR	[95% Conf.	Interval]
Year	1.10	1.07	1.12	1.18	1.16	1.20
Male	1.20	1.05	1.36	1.02	0.92	1.13
Age group**						
40-65	0.98	0.80	1.20	0.83	0.74	0,93
>80	0.82	0.72	0.95	0.99	0.85	1,16
Diabetes treatment***						
Oral antidiabetics	1.32	1.14	1.52	1.60	1.42	1,79
Additional insulin treatment	1.55	1.29	1.86	1.87	1.55	2,26
ACE inhibitors	1.31	1.14	1.50	1.16	1.03	1.30
Other antihypertensive drugs	1.23	1.07	1.42	1.25	1.12	1.39
Statin therapy	0.86	0.75	0.99	1.42	1.27	1.59
Anaemia	//	//	//	1.76	1.37	2.27
Osteoporosis	//	//	//	1.55	1.21	1.99
Psychological distress	//	//	//	1.27	1.10	1.47

Malignancy	//	//	//	1.35	1.12	1.63

** reference group age 66-80 years

*** reference group: no diabetes drugs

Figure 1. Ten-year evolution of the mean MDRD in patients with diagnosed CKD in 2010 according to the age group and presence or not of significant decline (SD).

Figura1a. in patients aged between 41 and 65 years in the year 2010.

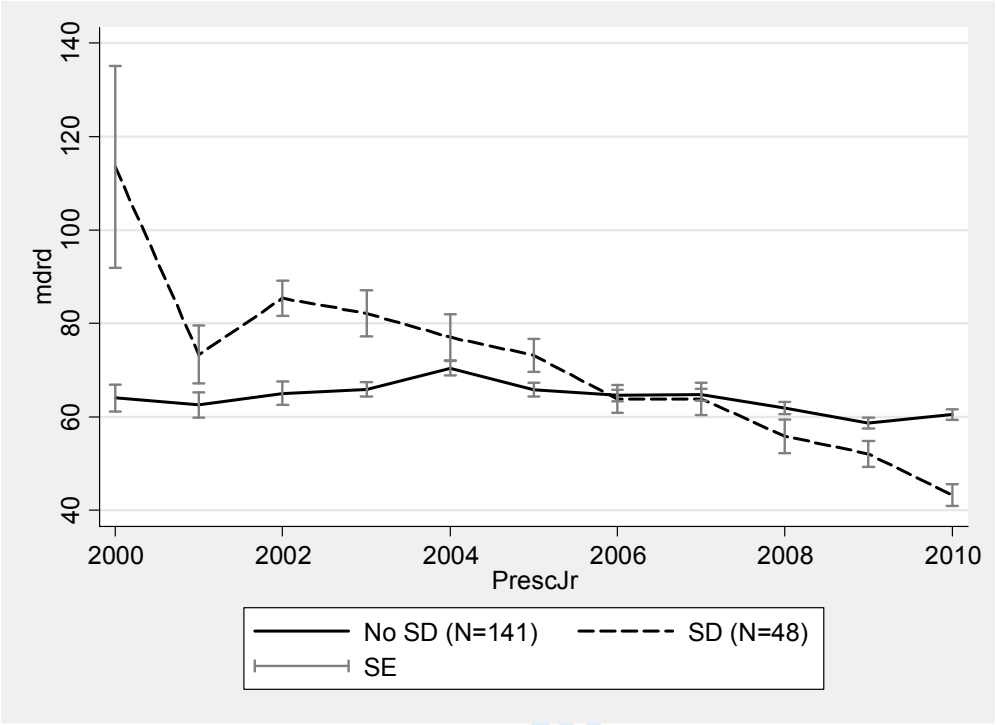


Figure 1b . in patients aged between 66 and 80 years in the year 2010.

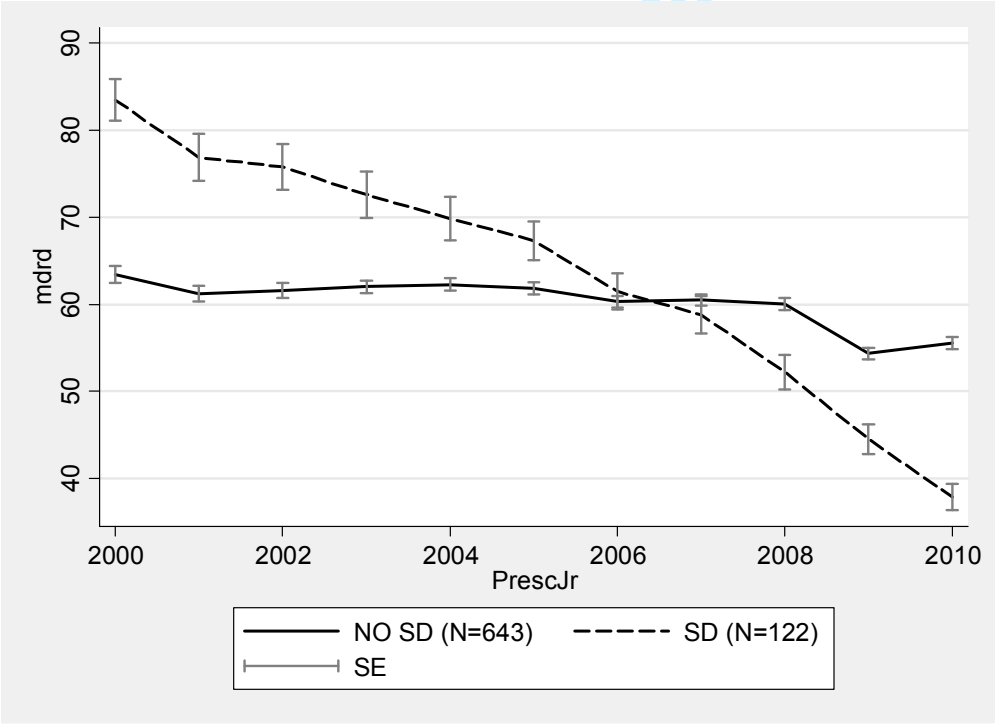
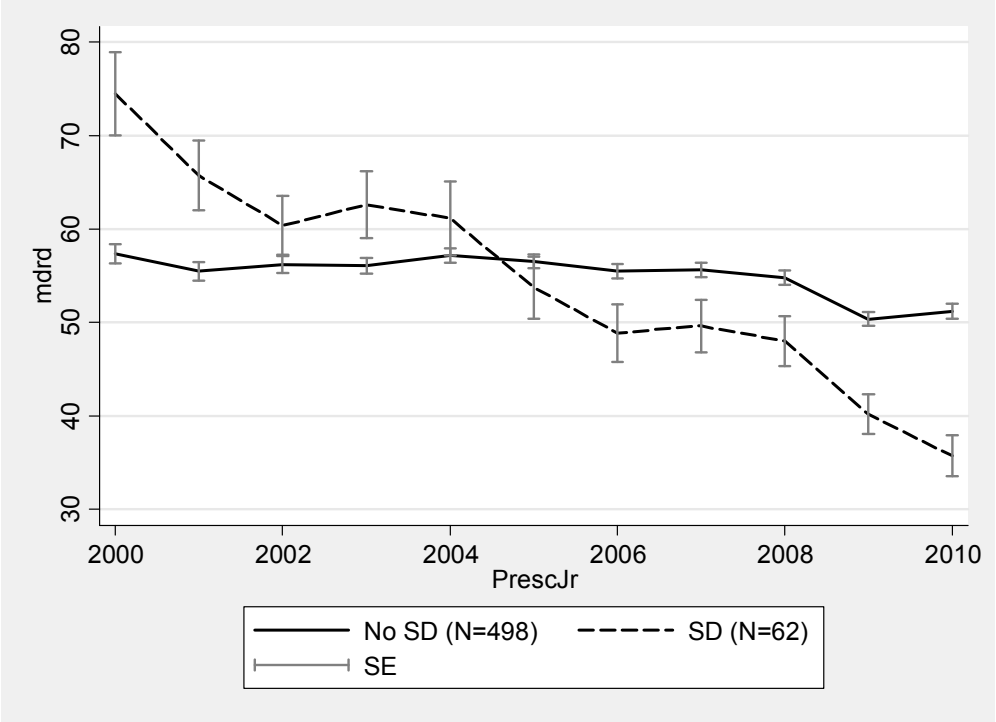


Figure 1c. In patients aged over 80 in the year 2010.



Contributorship

GG conceived and developed the study, made the analyses and wrote the manuscript ; FB Supervised the whole processing of conceiving, analyzing and writing ; GVP, CT and VVC helped to develop the study and double checked the statistical analyses ; CVDB and ED helped with the conception and development of the study, supervised the statistical analyses and wrote parts of the introduction and discussion section.

Data sharing

no additional data available

Competing Interests

None

Funding

None

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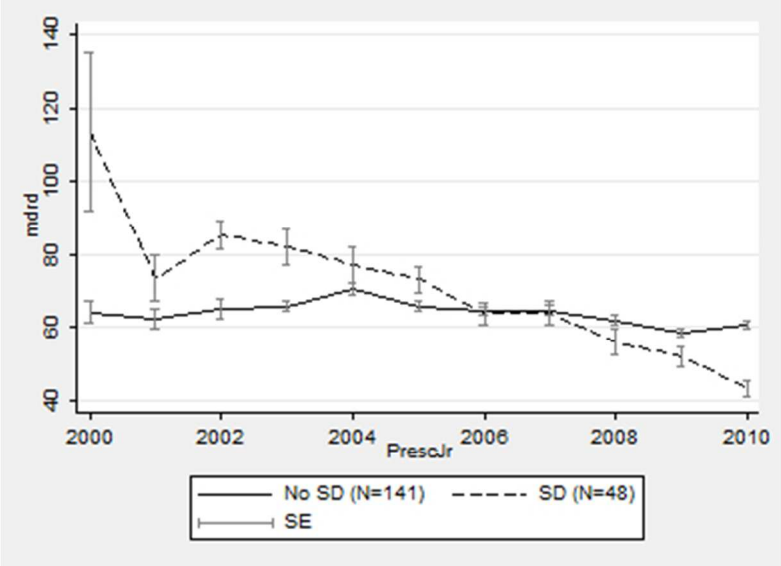

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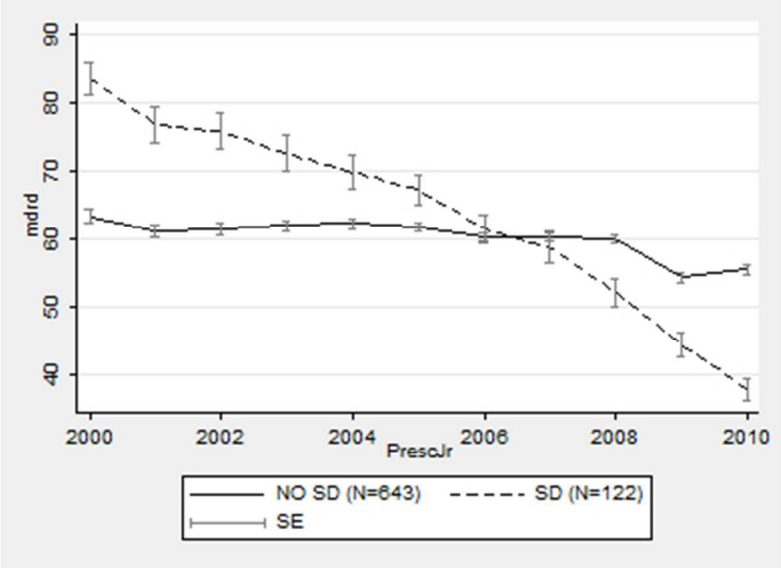

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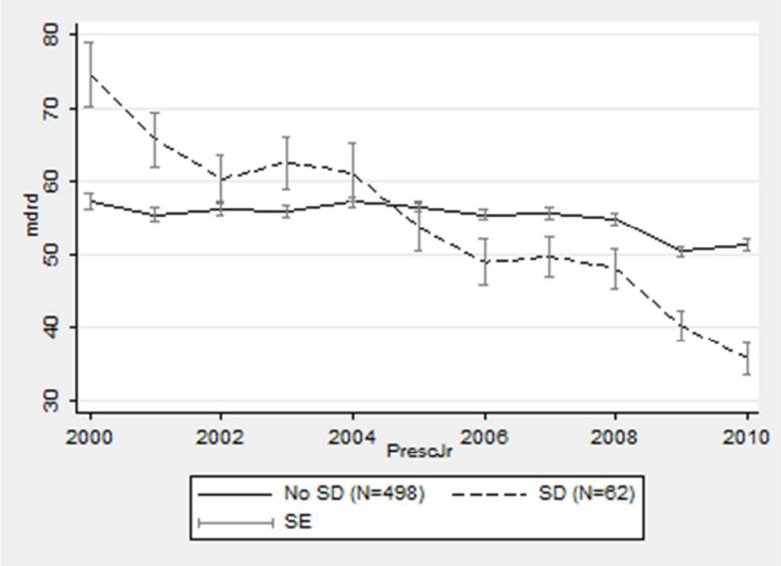

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
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
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
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
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
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
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	8-9

		confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
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	9-10
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	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	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	12

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.

Strenghts:

- The study population: a large primary care population that is representative of the population in Flanders with automatic inclusion of laboratory tests performed in primary care and a large proportion of the tests performed in hospitals.
- The database also contains all introduced diagnoses and most of the relevant clinical parameters.
- Strengths inherent to a retrospective design with long-term follow-up of the clinical and biological parameters. At least 2 eGFR measurements were available for all patients,
- Data analyses with longitudinal models incorporating between- and within-subject analyses with inclusion of timely changes in diagnoses and drug prescriptions.

Weaknesses:

- Lack of mortality data, data on renal replacement therapy and insufficient data on proteinuria/albuminuria and Body Mass Index (BMI).
- Weaknesses inherent to a Retrospective design and registry data: possible healthy survivor bias, no information about missing data and loss to follow-up

Long-tem evolution of renal function in patients with type 2 diabetes mellitus: a registry-based retrospective cohort study

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Renal medicine
Keywords:	Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Nephrology < INTERNAL MEDICINE, PRIMARY CARE

Long-term evolution of renal function in patients with type 2 diabetes mellitus: a registry-based retrospective cohort study

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Word count: abstract: 265 Body of text: 3276

3 tables, 1 figure

Key words: Type 2 diabetes Mellitus, Chronic Kidney Disease, eGFR decrease

Long-tem evolution of renal function in patients with type 2 diabetes mellitus: a registry-based retrospective cohort study

Objectives: To picture the 10-year evolution of renal function in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) and to describe the risk factors for severe decline (SD)

Setting: primary Registration network with 97 General Practitioners (GPs) working in 55 practices sending routinely collected patient data

Participants: From the database, we selected all patients aged 40 years or older with T2DM and at least two creatinine measurements in two different years with an interval of at least 3 months. Based on the last available value of eGFR calculated by the MDRD equation, patients were divided into grades of CKD. SD (decline of > 4 ml/min/year) and "certain drop" (CD, year-to-year decline > 10 ml/min) were determined in patients with CKD. Determinants of SD and CD were investigated with logistic regression and longitudinal logistic regression analysis, respectively.

Primary outcome measure: kidney function (MDRD)

Results: 4041 patients -1980 female - were included. Mean age was 71 years, mean diabetes duration 7.7 years; 1514 (38%) suffered from CKD, 231 (15%) presented with severe decline, 18% of the patients with CKD presented with 2 or more certain drops. Younger age, male gender, mean HbA1c and a higher number of certain drops were significantly associated with the presence of severe decline ($p<0.05$) ; statins and higher diastolic blood pressure were significantly associated with the absence of severe decline ($p<0.001$). ACE inhibitors, other antihypertensive drugs and anti-diabetic drugs including insulin therapy were specific determinants of certain drop.

Conclusions: CKD is highly prevalent in T2DM patients; a minority of patients evolve into severe decline that is associated with younger age, male gender, "certain drop" and manageable factors like blood pressure, blood glucose, associated drugs prescriptions and statin therapy. Further prospective observational and experimental research is needed to clarify the nature of those associations.

Abbreviations:

ATC: Anatomical Therapeutic Chemical Classification System
BMI: Body Mass Index
CKD: chronic kidney disease
CVD: cardiovascular disease
ESRD: end-stage renal disease
GP: general practice
GPs: general practitioners
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICPC-2: International Classification of Primary Care, second edition
MDRD: Modification of Diet in Renal Disease
NSAID: non steroidal anti-inflammatory drugs
NCD: number of certain drops
OAD: oral anti-diabetic drugs
OR: odds ratio
OS: overall slope
T2DM: type 2 diabetes mellitus
UK: United Kingdom
WHO: World Health Organisation

What is known

Chronic kidney disease is highly prevalent in patients with type 2 diabetes mellitus. Other risk factors are high blood pressure, obesity, older age, high cholesterol and a family history of chronic kidney disease. Poorly controlled diabetes increases the risk that chronic kidney disease will eventually lead to kidney failure.

Little is known about the long-term evolution of kidney function in patients with diabetes and CKD. Knowledge is also limited about supplementary risk factors of kidney deterioration in patients with T2DM and CKD.

What this study contributes

- Eighty-five percent of all patients with diabetes and CKD keep a stable kidney function for many years.
- Especially younger, male patients are at risk for severe decline of kidney function and evolution to renal failure.
- Long-term severe decline is also associated with poor blood glucose control and the presence of periods of sudden, rapid decline, itself associated with the prescription of ACE inhibitors, other antihypertensive agents and anti-diabetic drugs, including insulin therapy.
- Statin therapy and higher diastolic blood pressure were associated with lower odds of severe decline.

Strengths and weaknesses

Strengths:

- The study population: a large primary care population that is representative of the population in Flanders with automatic inclusion of laboratory tests performed in primary care and a large proportion of the tests performed in hospitals.
- The database also contains all introduced diagnoses and most of the relevant clinical parameters.
- Strengths inherent to a retrospective design with long-term follow-up of the clinical and biological parameters. At least 2 eGFR measurements were available for all patients,
- Data analyses with longitudinal models incorporating between- and within-subject analyses with inclusion of timely changes in diagnoses and drug prescriptions.

Weaknesses:

- Lack of mortality data, data on renal replacement therapy and insufficient data on proteinuria/albuminuria and Body Mass Index (BMI).
- Weaknesses inherent to a Retrospective design and registry data: possible healthy survivor bias, no information about missing data and loss to follow-up

- **Introduction**

The prevalence of both type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) is rapidly growing, with an expected doubling of the number of people with diabetes worldwide within the next 20 years (1). Patients with T2DM present a 25-40% lifetime risk of developing CKD (2). Patients with comorbid T2DM and CKD are at major risk for cardiovascular disease (CVD) and premature mortality (3). Thus, management of Type 2 Diabetes and CKD, as well as risk factor control seem to be a daunting challenge both for individual patients and for public health (4-6). Besides T2DM, major risk factors for CKD include cardiovascular disease, hypertension and obesity (4;7;8).

Despite a large prevalence of CKD, only a minority of those patients develop end stage renal disease (ESRD) (3). Besides kidney function at a given moment, the speed of decline of kidney function also plays a major role in the development of ESRD (9). Faster progression of CKD is also associated with higher mortality (10). Little is known about the risk factors in patients with CKD of rapid progression and serious complications (11). In addition, the use of eGFR alone, especially in elderly people, may lead to false positive diagnoses of CKD because a reduced eGFR at one point in time does not tell if it is a stable finding or a sign of a dynamic process of decline. Finally, severe decline may follow different 'routes' in different patients. In some patients, decline may be constant and gradual, while in other patients, stable periods may be alternate with "certain drops". In extreme situations, CKD may be a lifelong complication of acute kidney injury.(12)

T2DM is known to be by far the leading cause of ESRD in developed countries (13). Again, it is not known how many and what kind of patients with T2DM will develop ESRD. Very few studies have reported on the long-term evolution of renal function in patients with diabetes and determinants of deterioration of kidney function. Therefore, based on the data of a primary care registry, we wanted to investigate the severity of CKD in patients with T2DM. More specifically, we retrospectively analysed how renal function evolved over a period of 11 years - between 2000 and 2010 - in patients with T2DM and what risk factors were associated with deterioration of renal function.

Methodology

Design and data collection

We performed a retrospective cohort study on patients with type 2 diabetes using a general practicebased morbidity registration network (Intego). Intego started to collect data in 1994 but in the present study, data were used from 2000 until 2010. Ninety-seven GPs, all using the medical software program Medidoc®, collaborate in the Intego project. These 97 GPs work in 55 practices evenly spread over Flanders, Belgium. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The Intego GPs prospectively and routinely registered all new diagnoses together with new drug prescriptions, as well as laboratory test results and some background information (including gender and year of birth), using computer generated keywords internally linked to codes.

Using specially framed extraction software, new data were coded and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus automatically linked to the ICPC-2 (International Classification of Primary Care) and ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision). Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.

The inclusion criterion for the present study was the presence of the diagnosis of "type 2 diabetes" in the patient' file (ICPC-code T90). Exclusion criteria were an age below 40 years at the reported date of diagnosis of diabetes. Included patients also should have at least two creatinine (MDRD) measurements in two different calendar years, with a measurement interval of at least 3 months.

The variables of interest considered in this study included the age (year of birth), age at diagnosis of diabetes, creatinine, HbA1c, systolic and diastolic blood pressure, LDL cholesterol, gender and hypoglycaemic treatment group (diet, oral drugs only, combined oral antidiabetics (OAD) and insulin, insulin only), use of ACE inhibition, other antihypertensive medication, platelet inhibition, lipid lowering drugs, NSAID and the presence of different pathologies, such as cardiovascular disease (CVD) – defined as a history of stroke, ischaemic cardiac disease or peripheral arterial disease -, CKD, combined neuropathy and retinopathy, gout, anaemia, anxiety-depressive disorders, osteoporosis, dementia and malignancies.

For LDL-cholesterol and HbA1c, we withheld the last value of each year for longitudinal analysis. Both parameters are stable over time unless some intervention is carried out. Moreover, HbA1c represents a "weighted" average of blood glucose levels during the preceding 120 days with glucose levels in the preceding 30 days contributing about 50% to the final result (14). Taking the yearly average would include the danger of smoothing away hypoglycaemic treatment effects.

Regarding creatinine we took the average value of the last two measurements of each year in order to account for the important within-subject variability of this variable.

Finally, blood pressure is very prone to within-subject variability and to the "white coat hypertension" phenomenon, i.e. systematically increased values for all measurements taken by a professional and to increased values of the first measurement by a professional, improving after repetition (15). Therefore, we took into account the last three blood pressure measurements of each year and used the average of the lowest two values of these three measurements.

The eGFR was calculated with the Modification of Diet in Renal Disease (MDRD) formula: glomerular filtration rate (GFR) (mL/min/1.73 m2) = 186 × (Scr)−1.154 × (age)−0.203 × 0.742 (if female). We defined diagnosed CKD in patients if they presented two MDRD values <60 ml/min with an interval of at least three months. We used the classification system of the American Kidney Foundation to classify the patients: eGFR between 45 and 60 mL/min/1.73m2 = Grade 3A, eGFR between 30 and 45 mL/min/1.732 = Grade 3B, eGFR between 15 and 30 mL/min/1.73m2 = Grade 4 and eGFR <15 mL/min/1.73 m2 = Grade 5.

We calculated the overall slope (OS) of eGFR evolution as the difference between the last MDRD value and the first MDRD value divided by the number of interval years. Based on previous studies, patients were divided into three groups: no decline (OS≥0), mild to moderate decline(-4≤OS<0) and severe decline (OS<-4) ((10). We also calculated the year-on-year difference in MDRD in the longitudinal dataset and defined "certain drop" as a decrease in year-on-year MDRD >10ml. For each patient we counted the number of certain drops during the study period and defined it as the number of certain drops (NCD). Based on the results of previous work (16) as well as other studies (17), we divided the patients according to their age, with a first age group between 40 and 65 years, a second group between 66 and 80 years and a third group aged over 80 years.

Neither micro-albuminuria nor proteinuria were withheld in the analysis because of data collection issues (too few collections; no control on validity of measurement).

Statistical analysis

All analyses were performed with STATA 12.1 (StataCorp, Texas). Continuous parameters are shown as Mean±SD, binomial and multinomial parameters as percentages, and 95% CI. Significance tests were performed by t-test for continuous and χ^2 for dichotomous parameters. We built 3 regression models. The first model was a logistic model that analyzed the determinants of grade 5 CKD, used as a proxy for ESRD. The second model, a logistic regression model, aimed to examine the determinants of severe decline in patients with and without CKD. The last model, a longitudinal logistic model with random effects, examined the determinants of certain drop in patients with and without CKD.

Model building was performed in a concise manner. In the longitudinal logistic model, the individual patient was defined as panel variable. Each year was considered as 1 time unit with the year 2000 set as 0. All time evolving parameters (new diagnoses, new drugs prescriptions) were disaggregated

according to the year of introduction in the database (level 1). The only exceptions were "diabetes" and "diabetes duration", presented as level-2 parameters. In the logistic regression models, variables were aggregated. We used the overall mean values of HbA1c, SBP, DBP and LDL values as model variables. Drug prescriptions were accepted if they had been prescribed for three years or more. Only the diabetes treatment was based on the latest available data (year 2010). Diagnoses were accepted if they had if they have been included in the register, whatever the year.

In a first step, determinants were selected by binary models if $p<0.1$. Secondly, all determinants were put in 1 model and manually eliminated by stepwise backward regression. Only those determinants with $p<0.05$ were withheld in the models, except for age, gender and CKD (for which all models were adjusted).

Since all analyses are likelihood based, valid inferences can still be obtained under the assumption of random missingness, i.e., the fact that a variable is missing for a patient is unrelated to the outcome that would have been measured for that patient.

The Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (no ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079).

Results

The cohort included 4041 patients with T2DM of whom 1514 (38%) presented with CKD in 2010 and 988 (24%) with CKD grade 3a or higher. As to the number of creatinin levels, 126 patients (3%) had 2 measurements, 150 (4%) had 3 measurements, 187 (4%) had 4 measurements and 3578 (89%) had five or more measurements. As shown in table 1, patients with CKD significantly differ from patients without CKD for several parameters like age, gender, diabetes duration, history of CVD and non-diabetes related co-morbidity. Of those patients with CKD, 526 (35%) presented with grade 1 or 2, 534 (35%) with grade 3a, 311 (21%) with grade 3b, 110 (7%) with grade 4 and 33 (2%) with grade 5. As shown in figure 1, most patients with CKD remain stable for a long period. Indeed, 425 patients with CKD (28%) present no decline, 857 (56%) patients present moderate decline and 232 patients (15%) present severe decline. It is interesting to note that, in patients without CKD in 2010, only 7% present with severe decline.

CKD, including moderate or severe grade CKD were more prevalent in elderly people (table 2, p= 0.004). However, the proportion of patients with a severe decline tended to decrease with increasing age (40-65 yrs: 25% ; [19-32]- 66-80 yrs: 16%;[13-18] - >80 yrs: 11%;[9-14]). This decrease was not observed in people without CKD (40-65 yrs: 7.8%;[6,3-9,] – 65-80 yrs:7,1%;[0,5,6-8,6] - >80yrs 8.2%[5,3-11,9].

At least 1 certain drop was present in 59% (CI 95% 56-61) of patients with CKD and in 49% (CI95% 44-51) of patients without CKD, with 5 as a maximum number of certain drops. In patients with severe decline, prevalence of at least 1 certain drop was considerably higher than in patients without severe decline: 86% (CI 95% 81-90) versus 54% (CI 95% 51-57) in patients with CKD and 77% (CI 95% 70-83) versus 46% (CI 95% 44-48) in patients without CKD.

The first logistic regression model only showed 2 determinants for CKD grade 5: the baseline value of MDRD (OR= 0.95, CI 95% [0.98-0.99]) and presence of severe decline (OR= 27.71, CI 95% [3.62-212.16]).

The second logistic regression model showed a significant interaction between age group, gender and the number of certain drops (NCD) on the one hand, and CKD on significant decline on the other hand. Thus, different logistic models were built for patients with and without CKD (table 3). In patients with CKD, severe decline is associated with younger age, male gender (OR 1.73 [1.25-2.38]), mean HbA1c value (OR 1.33, [1.13-1.56]) and the number of certain drops (OR 2.31 [1.96-2.72]. Statin use [OR 0.69 [0.50-0.96] and DBP (OR 0.97 [0.94-1.00] are associated with lower odds of severe decline. In patients without CKD, age, gender and DBP do not have a significant effect on severe decline.

The longitudinal logistic model showed a significant interaction between time, age group, gender, anti-diabetic treatment, statin treatment and several co-morbidities (anaemia, osteoporosis, malignancy, anxious depression and gout) with CKD on the appearance of certain drop. Again, we built separate models for patients with and without CKD (table 4). Appearance of certain drop in patients with CKD was associated with male gender (OR 1.20 [1.05-1.36]), oral anti-diabetic treatment (OR 1.32 [1.14-1.52]), insulin treatment (OR 1.55 [1.29-1.86]), ACE inhibition (OR 1.31 [1.14-1.50]) and other antihypertensive treatment (OR 1.23 [1.07-1.42]), while age>80 (OR 0.82 [0.72-0.95]) and statin use (OR 0.86 [0.75-0.99]) were associated with lower odds (table 4). Associations were partly different in patients without CKD: younger age (40-65 years) was associated with lower odds, gender had no significant association, and statin treatment as well as several co-morbidities were associated with higher odds of certain drop.

Discussion

The results of our retrospective cohort study confirm previous findings about the high prevalence of CKD in patients with Type 2 Diabetes (18-20). However, although the fact that T2DM is a known risk factor for the development of CKD, this study also shows the presence of a great variability between T2DM patients regarding the decline in kidney function. Patients with CKD evolve in a different manner than patients without CKD and more people with CKD present with severe decline. Even in people with established CKD, only a minority (15%) of the patients present

with severe decline. As shown in figure 1, most patients remain stable for years. Interestingly in our study, severe decline and the 'baseline value' of MDRD are the only independent risk factors that are associated with progression to Grade 5 CKD, used as a proxy for end stage renal disease. Most patients with CKD - even with grade 3a, 3b or 4 - remain stable for many years. As such, the results of our study support the proposition of Al Aly and Cepeda that CKD should be defined in a dynamic way, taking into account both the CKD grade and the decline of kidney function (21). More specifically, age and gender interact with CKD in their effect on severe decline: in patients with CKD, but not in patients without CKD, severe decline is more prevalent in younger patients and in males. This observation may indicate that the current definition of CKD misclassifies some people, especially elderly and female persons, as patients suffering from chronic kidney disease.

In patients with CKD, severe decline is also associated with (potentially) manageable factors. Higher levels of HbA1c and a higher number of certain drops are associated with higher odds of severe decline, while higher levels of Diastolic Blood Pressure and statin therapy are associated with lower odds of severe decline. Certain drops can be interpreted as moments or periods of rapid decline alternating with longer periods of stable kidney function. The concept of certain drop is somehow controversial. Eventually, the obtained results could be due to random variation in the MDRD formula, but random variation cannot explain the differences in certain drop between patients with and without CKD and with and without severe decline. Moreover, our data show that not all patients with T2DM are equal with regards to CKD. The severity of decline of kidney function is an important factor, but what determines decline? The introduction of "certain drop" allows for showing that there are different ways in which the renal function can decline eventually suggesting different underlying causes. Indeed, some previous studies already suggested an association between ESRD and periods of rapid decline. (22;23) Certain drop may also be related to the findings of a meta-analysis that revealed that acute kidney injury is a determinant of CKD and ESRD (12). "Certain drop" and acute kidney injury may be two gradations of rapid collapse in kidney function responsible for an unfavourable evolution of kidney function in patients with CKD. However, patients without CKD are also prone to certain drop. Apparently, some people recover from brutal decline while others do not. From a clinical point of view, it would be interesting to quantify the impact of some determinants on severe decline and certain drop of kidney function, especially those which are manageable, such as nephrotoxic agents, infections, poor cardiovascular conditions or poor glucose control. Several drugs like ACE inhibitors, other antihypertensive drugs and anti-diabetic drugs including insulin therapy, are associated with higher odds of certain drop, while statins are associated with lower odds. In the framework of our study, it is not possible to interpret the nature of this relationship in causal terms. For instance, it is known that the initiation of ACE inhibitors can cause decline in kidney function in some people, but in our study, kidney function could eventually also deteriorate in some people despite ACE inhibition. The association between co-morbidity (anaemia, osteoporosis, anxious

depression and malignancy) and certain drop in patients without CKD, but not in patients with CKD, is another interesting result worthwhile exploring.

Other determinants, such as insufficient glycaemic control (higher HbA1c levels), may have a slowly damaging effect on the kidney function, while statins are associated with a protective effect. Curiously, a higher DBP is associated with lower odds of severe decline in patients with CKD, but not in patients without CKD. Literature is contradictory regarding the impact of DBP on kidney function decline. Some studies describe a negative association between higher DBP and kidney decline (24) while others mention a positive association (25). Our finding may be related to the conclusion that increased rates of pulse pressure are related to progression of renal impairment (26;27), even if in our study, pulse pressure was not an independent risk factor.

Only few studies have reported about kidney function decline in patients with T2DM. Zoppini (28) et al. reported a significant effect on kidney function decline of hypertension, increased HbA1c, longer diabetes duration, obesity, insulin treatment, microalbuminuria and macroalbuminuria. Cummings et al. found that age, mean systolic blood pressure, initial HbA1c, initial eGFR, and the number of HbA1c values were significant predictors of change in eGFR (29). Lin et al. did not find any association between blood lipids and kidney function decline (30). These outcomes are only partially in line with our results.

Strengths and weaknesses

The major strength of this study is the study population being a large primary care population that is representative of the population in Flanders. The Intego-population is comparable to the total Flemish population regarding age, gender and income distribution. Data on ethnicity are lacking but the registering practices are dispersed on the whole Flemish Region. (31). Comparison of the Intego diabetes population with other data sources shows comparable global prevalence and similar distribution of age-related prevalence.(32) The database automatically incorporates all data of laboratory tests performed in primary care and a large proportion of the tests performed in hospitals. The database also contains all introduced diagnoses and most of the relevant clinical parameters. It allows a follow up the long-term evolution of clinical and biological parameters. At least 2 eGFR measurements were available for all patients, and longitudinal models were applied to analyze the data, incorporating between- and within-subject analyses with inclusion of timely changes in diagnoses and drug prescriptions.

The study also has some weaknesses. First, we had no mortality data, nor data on renal replacement therapy. Secondly, the MDRD formula presents several weaknesses as a proxy for the real kidney function. E.g. loss of muscle mass in elderly patients may falsely give reduced estimates of renal function. However, the formula corrects for age that can act as a proxy for muscle mass. Since we were interested in the evolution of kidney function in the same persons, a change in formula does not

affect the model outcomes. Finally, although it is a well-known risk factor for the progression of CKD (33;34), we had no data on proteinuria/albuminuria because these were not frequently measured. We also did not have enough data on the Body Mass Index (BMI) to incorporate this variable in multivariate models. Using these data would have induced an important selection bias. However, laboratory tests were performed for clinical reasons. As such, the results give an idea of the "normal" working method of the GP: the lack of data on albuminuria and BMI gives an indication about a gap in the follow-up of patients with diabetes in primary care in Flanders. To determine "Severe Decline", we used the definition of Al Aly who found an association between Severe Decline based on this cut off value and mortality. However, in the literature, there is no consensus on how renal function decline should be reported and what cut off value should be used to determine 'Severity'. For example, Perkins and Krolewski used percentages to report renal function decline while Barzilay found that A 1 ml/min per 1.73 m2 per year eGFR decline had a borderline association with renal function decline in tests of cognitive function in patients with diabetes. We are thus in need of more research and a consensus procedure on this issue.

In conclusion, despite the large prevalence of CKD in patients with T2DM, only a minority present with rapid, severe decline and evolve into grade V CKD (used as proxy for ESRD). Kidney function in patients respectively with and without CKD evolves differently, with age and gender acting as interaction factors. In patients with CKD, but not in patients without CKD, kidney function decline tends to be more aggressive in younger and in male patients. Conversely, kidney function decline in elderly people, even if CKD is present, is not necessarily an aggressive, pathologic process. Our study also revealed the association of severe decline and/or certain drop with several potentially 'manageable' determinants like HBa1C, diastolic blood pressure, ACE inhibition, other antihypertensive agents and anti-diabetic drugs including insulin therapy. Some of them may rather be a description of the patients' severe multimorbid condition rather than the cause for a decline in renal function. Because of its retrospective character, this study is able to formulate hypotheses, but unable to determine any causal relationship. Further prospective observational and experimental research is needed to clarify the nature of those associations.

Competing interests: "All authors have completed the ICMJE uniform disclosure form at twww.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

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All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: no additional data available

Table 1. Characteristics of the diabetes population in 2010 for all patients, stratified according to the presence or not of CKD.

	All patients			No CKD (62%)			CKD (38%)			
Variable	Obs	Mean/%	SD	Obs	Mean/%	SD	Obs	Mean/%	SD	p
Male	4041	51%		2527	59%		1514	38%		<0.0001
Age	4041	71	11	2527	67	10	1514	77	9	<0.0001
diabetes duration	4041	7.7	6.3	2527	6.6	5.6	1514	9.6	6.9	<0.0001
HbA1c (%)	3128	6.9	1.0	1930	6.9	1,1	1198	6.9	1.0	0.056
HbA1c (mmol/mol)	3128	52	13	1930	52	13	1198	52	13	0.056
MDRD	3260	72	23	1991	85	17	1269	52	17	NA
severe decline	4041	10.4%		2527	7.5%		1514	15.3%		<0.001
% with ≥ 2 certain drop	4041	18.3%		2527	15.8%		1514	22.5%		<0.001
LDL cholesterol	2868	98	33	1823	100	33	1045	95	33	<0.001
SBP	2887	136	14	1848	135	14	1039	136	15	0.224
DBP	2887	79	8	1848	80	8	1039	77	8	<0.001
CVD	4041	29.1%		2527	22%		1514	40%		<0.001
Smoking	1254	14.7%		816	17%		438	10%		0.001
diabetes treatment	4041			2527			1514			
lifestyle only	1510	37.3%		896	35%		614	41%		
OAD	2013	49.8%		1385	55%		628	41%		<0.0001
Insulin	518	12.8%		246	10%		272	18%		<0.0001
antihypertensive	4041	54.5%		2527	51%		1514	60%		<0.0001
ACE inhibitors	4041	44.1%		2527	42%		1514	47%		0.007
platelet inhibition	4041	39.6%		2527	39%		1514	41%		0.145
lipid lowering	4041	48.1%		2527	49%		1514	46%		0.046
Anaemia	3927	3.5%		2472	2.5%		1455	5.2%		<0.001
Osteoporosis	3927	4.2%		2472	2.75%		1455	6.75%		<0.001
psychological distress	3927	11.3%		2472	10.5%		1455	12.7%		0.042
Dementia	3927	1.3%		2472	1.1%		1455	1.7%		0.107
Malignancy	3927	7.1%		2472	5.1%		1455	10.5%		<0.001
Gout	3927	8.0%		2472	6.9%		1455	9.9%		0.001

Table 2. Comparison of kidney-related parameters in patients with CKD, according to the age group.

Age in 2010	40-65 years*		66-80 years		> 80 years	
Variable	N=189/1345 (14%)		N= 765/1842 (41%)		N= 560/854 (66%)	
% with grade 3a -> 5	61%	[54-68]	64%	[60-67]	69%	[65-73]
% with CKD & severe decline	25%	[19-32]	16%	[13-18]	11%	[9-14]
% with CKD & two or more certain drops	27%	[21-34]	26%	[23-29]	16%	[13-20]
Mean MDRD in 2010	56	[54-58]	53	[51-54]	50	[48-51]
Mean CKD duration (yrs)	5.8	[5.3-6.5]	7.8	[7.4-8.1]	9.2	[8.9-9.7]

For dichotomous variables: % and exact (binomial) confidence interval of 95%

For continuous variables: mean value and confidence interval of 95%

Table 3. Logistic regression model analysing the odds of severe decline and its determinants in patients with (N= 1469) and without CKD (N=2385).

	Presence of CKD (N=1469)			**Absence of CKD (N=2385)**		
	Odds Ratio	[95% Conf.	Interval]	Odds Ratio	[95% Conf.	Interval]
age 66-80*	0.55	0.36	0.85	0.85	0.61	1.18
age>80*	0.41	0.25	0.67	1.02	0.63	1.66
Male	1.73	1.25	2.38	1.01	0.74	1.38
HbA1c (%)	1.33	1.13	1.56	1.20	1.05	1.37
Statin****	0.69	0.50	0.96	0.68	0.48	0.95
NCD	2.31	1.96	2.72	1.69	1.43	1.98
DBP (mm Hg)	0.97	0.94	1.00	//	//	//

* reference group age 40-65 years

***Drugs were included in patients' treatment if they had been prescribed for three years or more.

Table 4. Longitudinal logistic regression model with random effect analysing the odds of certain drop and its determinants in patients with CKD (N=1514) and without CKD (N= 3452).

	Patients with CKD (N=1514)			Patients without CKD (N=3452)		
	OR	[95% Conf.	Interval]	OR	[95% Conf.	Interval]
Year	1.10	1.07	1.12	1.18	1.16	1.20
Male	1.20	1.05	1.36	1.02	0.92	1.13
Age group**						
40-65	0.98	0.80	1.20	0.83	0.74	0,93
>80	0.82	0.72	0.95	0.99	0.85	1,16
Diabetes treatment***						
Oral antidiabetics	1.32	1.14	1.52	1.60	1.42	1,79
Additional insulin treatment	1.55	1.29	1.86	1.87	1.55	2,26
ACE inhibitors	1.31	1.14	1.50	1.16	1.03	1.30
Other antihypertensive drugs	1.23	1.07	1.42	1.25	1.12	1.39
Statin therapy	0.86	0.75	0.99	1.42	1.27	1.59
Anaemia	//	//	//	1.76	1.37	2.27
Osteoporosis	//	//	//	1.55	1.21	1.99
Psychological distress	//	//	//	1.27	1.10	1.47

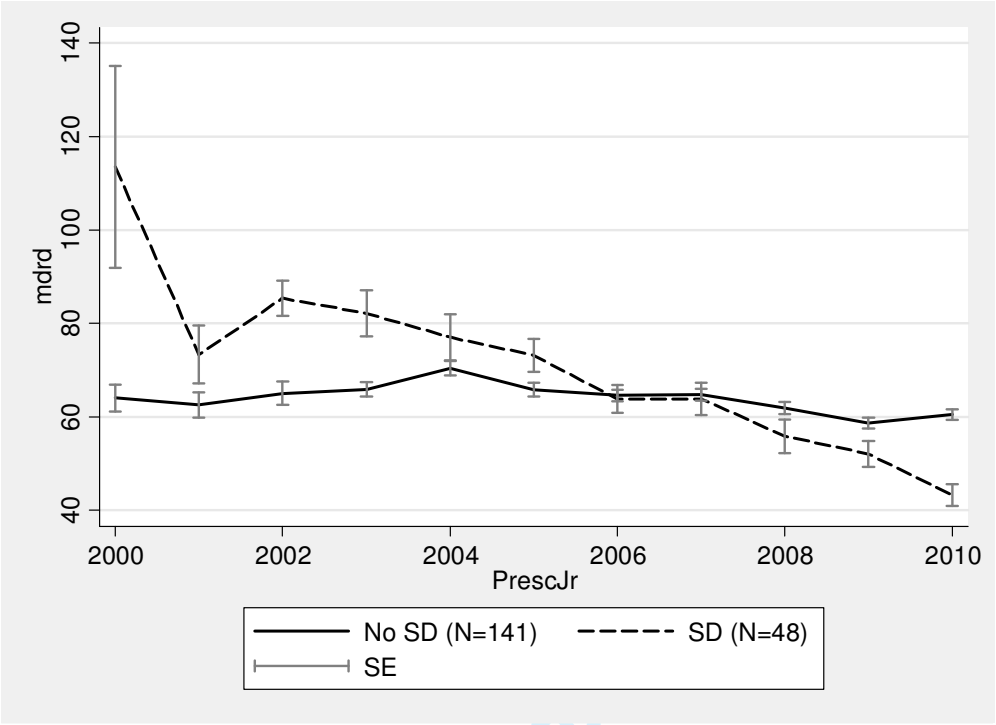
Malignancy	//	//	//	1.35	1.12	1.63

** reference group age 66-80 years

*** reference group: no diabetes drugs

Figure 1. Ten-year evolution of the mean MDRD in patients with diagnosed CKD in 2010 according to the age group and presence or not of significant decline (SD).

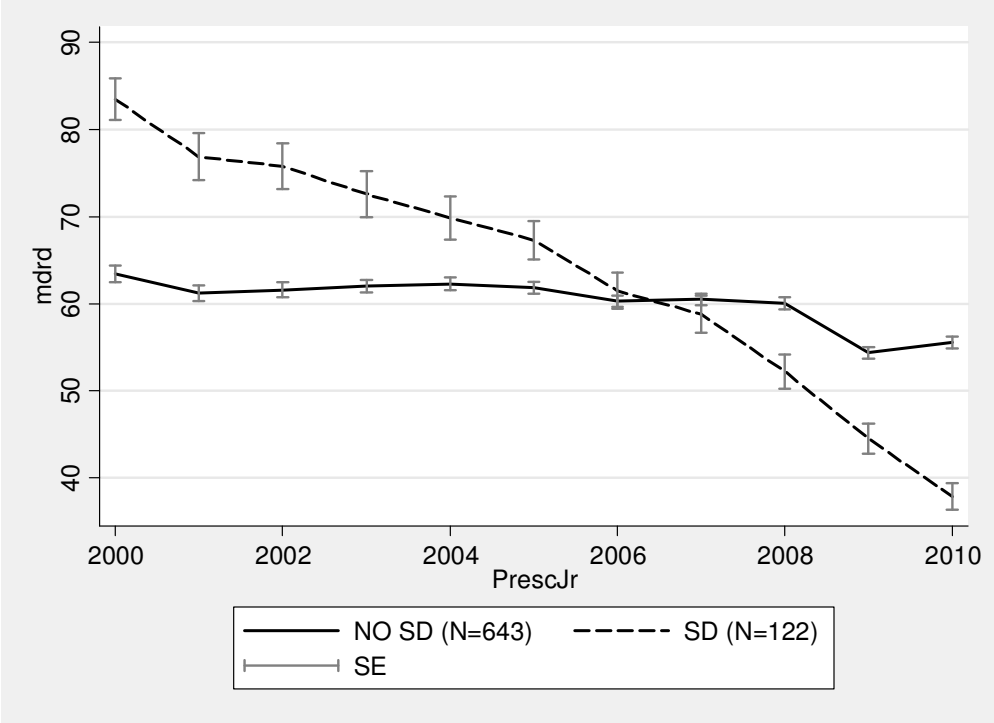
Figura1a. in patients aged between 45 and 65 years in the year 2010.



number of observations at each given year:

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
SD	11	12	20	31	35	57	61	84	98	108	109
No SD	271	329	360	477	545	670	698	757	822	874	983

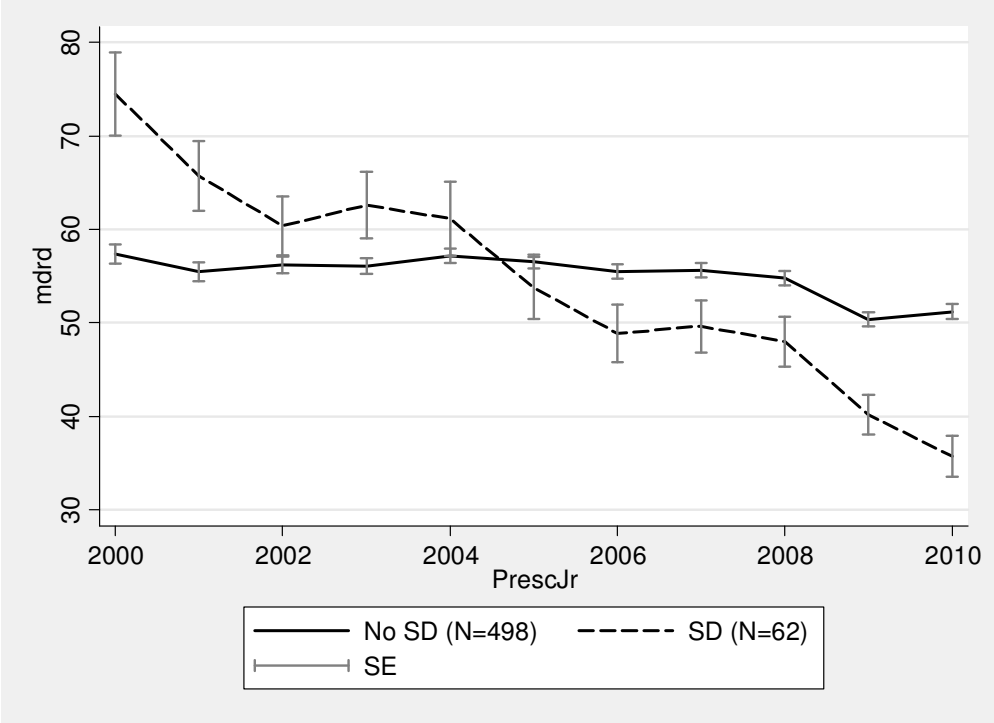
Figure 1b . in patients aged between 66 and 80 years in the year 2010.



Number of observations at each given year:

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
SD	40	41	57	56	72	88	105	117	137	154	148
No SD	628	721	787	937	1030	1166	1224	1272	1291	1360	1398

Figure 1c. In patients aged over 80 in the year 2010.



Number of observations at each given year:

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
SD	29	32	36	33	39	41	45	48	55	56	47
No SD	343	377	418	454	486	541	538	545	570	570	571

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Long-term evolution of renal function in patients with type 2 diabetes mellitus: a registry-based retrospective cohort study

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Abstract

Aim: To picture the 10-year evolution of renal function in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) and to describe the risk factors for severe decline (SD)

Method: In a primary care based morbidity registration network we selected all patients aged 40 years or older with T2DM and at least two creatinine measurements in two different years with an interval of at least 3 months. Based on the last available value of eGFR calculated by the MDRD equation, patients were divided into grades of CKD. SD (decline of > 4 ml/min/year) and "certain drop" (year-to-year decline > 10 ml/min) were determined in patients with CKD. Determinants of severe decline and certain drop were investigated with logistic regression and longitudinal logistic regression analysis, respectively.

Results: 4041 patients -1980 female - were included. Mean age was 71 years, mean diabetes duration 7.7 years; 1514 (38%) suffered from CKD, 231 (15%) presented with severe decline, 18% of the patients with CKD presented with 2 or more certain drops. Younger age, male gender, mean HbA1c and a higher number of certain drops were significantly associated with the presence of severe decline ($p<0.05$) ; statins and higher diastolic blood pressure were significantly associated with the absence of severe decline ($p<0.001$). ACE inhibitors, other antihypertensive drugs and anti-diabetic drugs including insulin therapy were specific determinants of certain drop.

Conclusions: CKD is highly prevalent in T2DM patients; a minority of patients evolve into severe decline that is associated with younger age, male gender and manageable factors like blood pressure, blood glucose, associated drugs prescriptions and statin therapy.

Objectives: To picture the 10-year evolution of renal function in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) and to describe the risk factors for severe decline (SD)

Setting: primary Registration network with 97 General Practitioners (GPs) working in 55 practices sending routinely collected patient data

Participants: From the database, we selected all patients aged 40 years or older with T2DM and at least two creatinine measurements in two different years with an interval of at least 3 months. Based on the last available value of eGFR calculated by the MDRD equation, patients were divided into grades of CKD. SD (decline of > 4 ml/min/year) and "certain drop" (CD, year-to-year decline > 10 ml/min) were determined in patients with CKD. Determinants of SD and CD were investigated with logistic regression and longitudinal logistic regression analysis, respectively.

Primary outcome measure: kidney function (MDRD)

Results: 4041 patients -1980 female - were included. Mean age was 71 years, mean diabetes duration 7.7 years; 1514 (38%) suffered from CKD, 231 (15%) presented with severe decline, 18% of the patients with CKD presented with 2 or more certain drops. Younger age, male gender, mean HbA1c and a higher number of certain drops were significantly associated with the presence of severe decline ($p<0.05$) ; statins and higher diastolic blood pressure were significantly associated with the absence of severe decline ($p<0.001$). ACE inhibitors, other antihypertensive drugs and anti-diabetic drugs including insulin therapy were specific determinants of certain drop.

Conclusions: CKD is highly prevalent in T2DM patients; a minority of patients evolve into severe decline that is associated with younger age, male gender, "certain drop" and manageable factors like blood pressure, blood glucose, associated drugs prescriptions and statin therapy. Further prospective observational and experimental research is needed to clarify the nature of those associations.

Abbreviations:

ATC: Anatomical Therapeutic Chemical Classification System
BMI: Body Mass Index
CD: Certain Drop
CKD: chronic kidney disease
CVD: cardiovascular disease
ESRD: end-stage renal disease
GP: general practice
GPs: general practitioners
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICPC-2: International Classification of Primary Care, second edition
MDRD: Modification of Diet in Renal Disease
NSAID: non steroidal anti-inflammatory drugs
NCD: number of certain drops
OAD: oral anti-diabetic drugs
OR: odds ratio
OS: overall slope
T2DM: type 2 diabetes mellitus
UK: United Kingdom
WHO: World Health Organisation

What is known

Chronic kidney disease is highly prevalent in patients with type 2 diabetes mellitus. Other risk factors are high blood pressure, obesity, older age, high cholesterol and a family history of chronic kidney disease. Poorly controlled diabetes increases the risk that chronic kidney disease will eventually lead to kidney failure.

Little is known about the long-term evolution of kidney function in patients with diabetes and CKD. Knowledge is also limited about supplementary risk factors of kidney deterioration in patients with T2DM and CKD.

What this study contributes

- Eighty-five percent of all patients with diabetes and CKD keep a stable kidney function for many years.
- Especially younger, male patients are at risk for severe decline of kidney function and evolution to renal failure.
- Long-term severe decline is also associated with poor blood glucose control and the presence of periods of sudden, rapid decline, itself associated with the prescription of ACE inhibitors, other antihypertensive agents and anti-diabetic drugs, including insulin therapy.
- Statin therapy and higher diastolic blood pressure were associated with lower odds of severe decline.

Strengths and weaknesses

Strengths:

- The study population: a large primary care population that is representative of the population in Flanders with automatic inclusion of laboratory tests performed in primary care and a large proportion of the tests performed in hospitals.
- The database also contains all introduced diagnoses and most of the relevant clinical parameters.
- Strengths inherent to a retrospective design with long-term follow-up of the clinical and biological parameters. At least 2 eGFR measurements were available for all patients,
- Data analyses with longitudinal models incorporating between- and within-subject analyses with inclusion of timely changes in diagnoses and drug prescriptions.

Weaknesses:

- Lack of mortality data, data on renal replacement therapy and insufficient data on proteinuria/albuminuria and Body Mass Index (BMI).
- Weaknesses inherent to a Retrospective design and registry data: possible healthy survivor bias, no information about missing data and loss to follow-up

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- **Introduction**

The prevalence of both type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) is rapidly growing, with an expected doubling of the number of people with diabetes worldwide within the next 20 years (1)~~(1)~~. Patients with T2DM present a 25-40% lifetime risk of developing CKD (2)~~(2)~~. Patients with comorbid T2DM and CKD are at major risk for cardiovascular disease (CVD) and premature mortality (3)~~(3)~~. Thus, management of Type 2 Diabetes and CKD, as well as risk factor control seem to be a daunting challenge both for individual patients and for public health (4-6)~~(4-6)~~. Besides T2DM, major risk factors for CKD include cardiovascular disease, hypertension and obesity (4;7;8)~~(4;7;8)~~.

Despite a large prevalence of CKD, only a minority of those patients develop end stage renal disease (ESRD) (3)~~(3)~~. Besides kidney function at a given moment, the speed of decline of kidney function also plays a major role in the development of ESRD (9)~~(9)~~. Faster progression of CKD is also associated with higher mortality (10)~~(10)~~. Little is known about the risk factors in patients with CKD of rapid progression and serious complications (11)~~(11)~~. In addition, the use of eGFR alone, especially in elderly people, may lead to false positive diagnoses of CKD because ~~the decreased eGFR could just represent an age-related functional decline.~~ a reduced eGFR a one point in time does not tell if it is a stable finding or a sign of a dynamic process of decline. Finally, severe decline may follow different 'routes' in different patients. In some patients, decline may be constant and gradual, while in other patients, stable periods may be alternate with "certain drops". In extreme situations, CKD may be a lifelong complication of acute kidney injury.(12)

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T2DM is known to be by far the leading cause of ESRD in developed countries (13)~~(12)~~. Again, it is not known how many and what kind of patients with T2DM will develop ESRD. Very few studies have reported on the long-term evolution of renal function in patients with diabetes and determinants of deterioration of kidney function. Therefore, based on the data of a primary care registry, we wanted to investigate the severity of CKD in patients with T2DM. More specifically, we retrospectively analysed how renal function evolved over a period of 11 years - between 2000 and 2010 - in patients with T2DM and what risk factors were associated with deterioration of renal function.

Methodology

Design and data collection

We performed a retrospective cohort study on patients with type 2 diabetes using a general practicebased morbidity registration network (Intego). Intego started to collect data in 1994 but in the present study, data were used from 2000 until 2010. Ninety-seven GPs, all using the medical software program Medidoc®, collaborate in the Intego project. These 97 GPs work in 55 practices evenly spread over Flanders, Belgium. GPs applied for inclusion in the registry. Before acceptance of their data, registration performance was audited using a number of algorithms that compared their results with all other applicants. Only the data of the practices with an optimal registration performance were included in the database. The Intego GPs prospectively and routinely registered all new diagnoses together with new drug prescriptions, as well as laboratory test results and some background information (including gender and year of birth), using computer generated keywords internally linked to codes.

Using specially framed extraction software, new data were coded and collected from the GPs' personal computers and entered into a central database. Registered data were continuously updated and historically accumulated for each patient. New diagnoses were classified according to a very detailed thesaurus automatically linked to the ICPC-2 (International Classification of Primary Care) and ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision). Drugs were classified according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system.

The inclusion criterion for the present study was the presence of the diagnosis of "type 2 diabetes" in the patient' file (ICPC-code T90). Exclusion criteria were an age below 40 years at the reported date of diagnosis of diabetes. Included patients also should have at least two creatinine (MDRD) measurements in two different calendar years, with a measurement interval of at least 3 months.

The variables of interest considered in this study included the age (year of birth), age at diagnosis of diabetes, creatinine, HbA1c, systolic and diastolic blood pressure, LDL cholesterol, gender and hypoglycaemic treatment group (diet, oral drugs only, combined oral antidiabetics (OAD) and insulin, insulin only), use of ACE inhibition, other antihypertensive medication, platelet inhibition, lipid lowering drugs, NSAID and the presence of different pathologies, such as cardiovascular disease (CVD) – defined as a history of stroke, ischaemic cardiac disease or peripheral arterial disease -, CKD, combined neuropathy and retinopathy, gout, anaemia, anxiety-depressive disorders, osteoporosis, dementia and malignancies.

For LDL-cholesterol and HbA1c, we withheld the last value of each year for longitudinal analysis. Both parameters are stable over time unless some intervention is carried out. Moreover, HbA1c represents a "weighted" average of blood glucose levels during the preceding 120 days with glucose levels in the preceding 30 days contributing about 50% to the final result (14)~~(13)~~. ~~As such, HbA1c only changes progressively over three months when treatment changes.~~ Taking the yearly average

would include the danger of smoothing away hypoglycaemic treatment effects.

Regarding creatinine we took the average value of the last two measurements of each year in order to account for the important within-subject variability of this variable.

Finally, blood pressure is very prone to within-subject variability and to the "white coat hypertension" phenomenon, i.e. systematically increased values for all measurements taken by a professional and to increased values of the first measurement by a professional, improving after repetition (15)~~(14)~~. Therefore, we took into account the last three blood pressure measurements of each year and used the average of the lowest two values of these three measurements.

The eGFR was calculated with the Modification of Diet in Renal Disease (MDRD) formula: glomerular filtration rate (GFR) (mL/min/1.73 m2) = 186 × (Scr)−1.154 × (age)−0.203 × 0.742 (if female). We defined diagnosed CKD in patients if they presented two MDRD values <60 ml/min with an interval of at least three months. We used the classification system of the American Kidney Foundation to classify the patients: eGFR between 45 and 60 mL/min/1.73m2 = Grade 3A, eGFR between 30 and 45 mL/min/1.732 = Grade 3B, eGFR between 15 and 30 mL/min/1.73m2 = Grade 4 and eGFR <15 mL/min/1.73 m2 = Grade 5. ~~In this definition, patients with CKD stages 1 and 2 were excluded from analysis.~~

We calculated the overall slope (OS) of eGFR evolution as the difference between the last MDRD value and the first MDRD value divided by the number of interval years. Based on previous studies, patients were divided into three groups: no decline (OS≥0), mild to moderate decline(-4≤OS<0) and severe decline (OS<-4) ((10)~~(10)~~. We also calculated the year-on-year difference in MDRD in the longitudinal dataset and defined "certain drop" as a decrease in year-on-year MDRD >10ml. For each patient we counted the number of certain drops during the study period and defined it as the number of certain drops (NCD). Based on the results of previous work(16), as well as other studies(17)w~~W~~e ~~also~~ divided the patients according to their age, with a first age group between 40 and 65 years, a second group between 66 and 80 years and a third group aged over 80 years.

Neither micro-albuminuria nor proteinuria were withheld in the analysis because of data collection issues (too few collections; no control on validity of measurement).

Statistical analysis

All analyses were performed with STATA 12.1 (StataCorp, Texas). Continuous parameters are shown as Mean±SD, binomial and multinomial parameters as percentages, and 95% CI. Significance tests were performed by t-test for continuous and χ^2 for dichotomous parameters. We built 3 regression models. The first model was a logistic model that analyzed the determinants of grade 5 CKD, used as a proxy for ESRD. The second model, a logistic regression model, aimed to examine the determinants of severe decline in patients with and without CKD. The last model, a longitudinal logistic model with random effects, examined the determinants of certain drop in patients with and without CKD.

Model building was performed in a concise manner. In the longitudinal logistic model, the individual patient was defined as panel variable. Each year was considered as 1 time unit with the year 2000 set as 0. All time evolving parameters (new diagnoses, new drugs prescriptions) were disaggregated according to the year of introduction in the database (level 1). The only exceptions were "diabetes" and "diabetes duration", presented as level-2 parameters. In the logistic regression models, variables were aggregated. We used the overall mean values of HbA1c, SBP, DBP and LDL values as model variables. Drug prescriptions were accepted if they had been prescribed for three years or more. Only the diabetes treatment was based on the latest available data (year 2010). Diagnoses were accepted if they had if they have been included in the register, whatever the year.

In a first step, determinants were selected by binary models if $p<0.1$. Secondly, all determinants were put in 1 model and manually eliminated by stepwise backward regression. Only those determinants with $p<0.05$ were withheld in the models, except for age, gender and CKD (for which all models were adjusted).

Since all analyses are likelihood based, valid inferences can still be obtained under the assumption of random missingness, i.e., the fact that a variable is missing for a patient is unrelated to the outcome that would have been measured for that patient.

The Intego procedures were approved by the ethical review board of the Medical School of the Catholic University of Leuven (no ML 1723) and by the Belgian Privacy Commission (no SCSZG/13/079).

Results

The cohort included 4041 patients with T2DM of whom 1514 (38%) presented with CKD in 2010 and 988 (24%) with CKD grade 3a or higher. As to the number of creatinin levels, 126 patients (3%) had 2 measurements, 150 (4%) had 3 measurements, 187 (4%) had 4 measurements and 3578 (89%) had five or more measurements. As shown in table 1, patients with CKD ~~they~~ significantly differ from patients without CKD for several parameters like age, gender, diabetes duration, history of CVD and non diabetes related co-morbidity. Of those patients with CKD, 526 (35%) presented with grade 1 or 2, 534 (35%) with grade 3a, 311 (21%) with grade 3b, 110 (7%) with grade 4 and 33 (2%) with grade 5.

As shown in figure 1, most patients with CKD remain stable for a long period. Indeed, 425 patients with CKD (28%) present no decline, 857 (56%) patients present moderate decline and 232 patients (15%) present severe decline. It is interesting to note that, in patients without CKD in 2010, only 7% present with severe decline.

CKD, including moderate or severe grade CKD were more prevalent in elderly people (table 2, p= 0.004). However, the proportion of patients with a severe decline tended to decrease with increasing age (40-65 yrs:25% ; [19-32]- 66-80 yrs: 16%;[13-18] - >80 yrs: 11%;[9-14]). This decrease was not

observed in people without CKD (40-65 yrs: 7.8%;[6,3-9,] – 65-80 yrs:7,1%;[0,5,6-8,6] - >80yrs 8.2%[5,3-11,9].

At least 1 certain drop was present in 59% (CI 95% 56-61) of patients with CKD and in 49% (CI95% 44-51) of patients without CKD, with 5 as a maximum number of certain drops. In patients with severe decline, prevalence of at least 1 certain drop was considerably higher than in patients without severe decline: 86% (CI 95% 81-90) versus 54% (CI 95% 51-57) in patients with CKD and 77% (CI 95% 70-83) versus 46% (CI 95% 44-48) in patients without CKD.

The first logistic regression model only showed 2 determinants for CKD grade 5: the baseline value of MDRD (OR= 0.95, CI 95% [0.98-0.99]) and presence of severe decline (OR= 27.71, CI 95% [3.62-212.16]).

The second logistic regression model showed a significant interaction between age group, gender and the number of certain drops (NCD) on the one hand, and CKD on significant decline on the other hand. Thus, different logistic models were built for patients with and without CKD (table 3). In patients with CKD, severe decline is associated with younger age, male gender (OR 1.73 [1.25-2.38]), mean HbA1c value (OR 1.33, [1.13-1.56]) and the number of certain drops (OR 2.31 [1.96-2.72]. Statin use [OR 0.69 [0.50-0.96] and DBP (OR 0.97 [0.94-1.00] are associated with lower odds of severe decline. In patients without CKD, age, gender and DBP do not have a significant effect on severe decline.

The longitudinal logistic model showed a significant interaction between time, age group, gender, anti-diabetic treatment, statin treatment and several co-morbidities (anaemia, osteoporosis, malignancy, anxious depression and gout) with CKD on the appearance of certain drop. Again, we built separate models for patients with and without CKD (table 4). Appearance of certain drop in patients with CKD was associated with male gender (OR 1.20 [1.05-1.36]), oral anti-diabetic treatment (OR 1.32 [1.14-1.52]), insulin treatment (OR 1.55 [1.29-1.86]), ACE inhibition (OR 1.31 [1.14-1.50]) and other antihypertensive treatment (OR 1.23 [1.07-1.42]), while age>80 (OR 0.82 [0.72-0.95]) and statin use (OR 0.86 [0.75-0.99]) were associated with lower odds (table 4). Associations were partly different in patients without CKD: younger age (40-65 years) was associated with lower odds, gender had no significant association, and statin treatment as well as several co-morbidities were associated with higher odds of certain drop.

Discussion

The results of our retrospective cohort study confirm previous findings about the high prevalence of CKD in patients with Type 2 Diabetes (18-20)~~(15-17)~~. However, although the fact that T2DM is a known risk factor for the development of CKD, this study also shows the presence of a

great variability between T2DM patients regarding the decline in kidney function. Patients with CKD evolve in a different manner than patients without CKD and more people with CKD present with severe decline. Even in people with established CKD, only a minority (15%) of the patients present with severe decline. As shown in figure 1, most patients remain stable for years. Interestingly in our study, severe decline and the 'baseline value' of MDRD are the only independent risk factors that are associated with progression to Grade 5 CKD, used as a proxy for end stage renal disease. Most patients with CKD - even with grade 3a, 3b or 4 - remain stable for many years. As such, the results of our study support the proposition of Al Aly and Cepeda that CKD should be defined in a dynamic way, taking into account both the CKD grade and the decline of kidney function (21)~~(18)~~. More specifically, age and gender interact with CKD in their effect on severe decline: in patients with CKD, but not in patients without CKD, severe decline is more prevalent in younger patients and in males. This observation may indicate that the current definition of CKD misclassifies some people, especially elderly and female persons, as patients suffering from chronic kidney disease.

In patients with CKD, severe decline is also associated with (potentially) manageable factors. Higher levels of HbA1c and a higher number of ~~certain drop~~certain drops are associated with higher odds of severe decline, while higher levels of Diastolic Blood Pressure and statin therapy are associated with lower odds of severe decline. C~~c~~ertain drops can be interpreted as moments or periods of rapid decline alternating with longer periods of stable kidney function. The concept of certain drop is somehow controversial. Eventually, the obtained results could be due to random variation in the MDRD formula, but random variation cannot explain the differences in certain drop between patients with and without CKD and with and without severe decline. Moreover, our data show that not all patients with T2DM are equal with regards to CKD. The severity of decline of kidney function is an important factor, but what determines decline? The introduction of "certain drop" allows for showing that there are different ways in which the renal function can decline eventually suggesting different underlying causes. Indeed, s~~S~~ome previous studies already suggested an association between ESRD and periods of rapid decline. (22;23)~~(19;20)~~ Certain drop may also be related to the findings of a meta-analysis that revealed that acute kidney injury is a determinant of CKD and ESRD (12)~~(21)~~. "Certain drop" and acute kidney injury may be two gradations of rapid collapse in kidney function responsible for an unfavourable evolution of kidney function in patients with CKD. However, patients without CKD are also prone to certain drop. Apparently, some people recover from brutal decline while others do not. From a clinical point of view, it would be interesting to quantify the impact of some determinants on severe decline and certain drop of kidney function, especially those which are manageable, such as nephrotoxic agents, infections, poor cardiovascular conditions or poor glucose control. Several drugs like ACE inhibitors, other antihypertensive drugs and anti-diabetic drugs including insulin therapy, are associated with higher odds of certain drop, while statins are associated with lower odds. In the framework of our study, it is not possible to interpret the nature of this relationship in causal terms. For instance, it is known that the initiation of ACE inhibitors can cause

decline in kidney function in some people, but in our study, kidney function could eventually also deteriorate in some people despite ACE inhibition. The association between co-morbidity (anaemia, osteoporosis, anxious depression and malignancy) and certain drop in patients without CKD, but not in patients with CKD, is another interesting result worthwhile exploring.

Other determinants, such as insufficient glycaemic control (higher HbA1c levels), may have a slowly damaging effect on the kidney function, while statins are associated with a protective effect. Curiously, a higher DBP is associated with lower odds of severe decline in patients with CKD, but not in patients without CKD. Literature is contradictory regarding the impact of DBP on kidney function decline. Some studies describe a negative association between higher DBP and kidney decline (24)~~(22)~~ while others mention a positive association (25)~~(23)~~. Our finding may be related to the conclusion that increased rates of pulse pressure are related to progression of renal impairment (26;27)~~(24;25)~~, even if in our study, pulse pressure was not an independent risk factor.

Only few studies have reported about kidney function decline in patients with T2DM. Zoppini (28)~~(26)~~ et al. reported a significant effect on kidney function decline of hypertension, increased HbA1c, longer diabetes duration, obesity, insulin treatment, microalbuminuria and macroalbuminuria. Cummings et al. found that age, mean systolic blood pressure, initial HbA1c, initial eGFR, and the number of HbA1c values were significant predictors of change in eGFR (29)~~(27)~~. Lin et al. did not find any association between blood lipids and kidney function decline (30)~~(28)~~. These outcomes are only partially in line with our results.

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Strengths and weaknesses

The major strength of this study is the study population being a large primary care population that is representative of the population in Flanders. The Intego-population is comparable to the total Flemish population regarding age, gender and income distribution. Data on ethnicity are lacking but he registering practices are dispersed on the whole Flemish Region. -(31). Comparison of the Intego diabetes population with other data sources shows comparable global prevalence and similar distribution of age-related prevalence.(32) The database automatically incorporates all data of laboratory tests performed in primary care and a large proportion of the tests performed in hospitals. The database also contains all introduced diagnoses and most of the relevant clinical parameters. It allows a follow up the long-term evolution of clinical and biological parameters. At least 2 eGFR measurements were available for all patients, and longitudinal models were applied to analyze the data, incorporating between- and within-subject analyses with inclusion of timely changes in diagnoses and drug prescriptions.

The study also has some weaknesses. First, we had no mortality data, nor data on renal replacement therapy. Secondly, the MDRD formula presents several weaknesses as a proxy for the real kidney function. E.g. loss of muscle mass in elderly patients may falsely give reduced estimates of renal

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function. However, the formula corrects for age that can act as a proxy for muscle mass. Since we were interested in the evolution of kidney function in the same persons, a change in formula does not affect the model outcomes. Finally~~Secondly~~, although it is a well-known risk factor for the progression of CKD (33;34), we had no data on proteinuria/albuminuria because these were not frequently measured. We also did not have enough data on the Body Mass Index (BMI) to incorporate this variable in multivariate models. Using these data would have induced an important selection bias. However, laboratory tests were performed for clinical reasons. As such, the results give an idea of the "normal" working method of the GP: the lack of data on albuminuria and BMI gives an indication about a gap in the follow-up of patients with diabetes in primary care in Flanders. To determine "Severe Decline", we used the definition of Al Aly who found an association between Severe Decline based on this cut off value and mortality. However, in the literature, there is no consensus on how renal function decline should be reported and what cut off value should be used to determine 'Severity'. For example, Perkins and Krolewski used percentages to report renal function decline while Barzilay found that A 1 ml/min per 1.73 m2 per year eGFR decline had a borderline association with renal function decline in tests of cognitive function in patients with diabetes. We are thus in need of more research and a consensus procedure on this issue.

In conclusion, despite the large prevalence of CKD in patients with T2DM, only a minority present with rapid, severe decline and evolve into grade V CKD (used as proxy for ESRD). Kidney function in patients respectively with and without CKD evolves differently, with age and gender acting as interaction factors. In patients with CKD, but not in patients without CKD, kidney function decline tends to be more aggressive in younger and in male patients. Conversely, kidney function decline in elderly people, even if CKD is present, is not necessarily an aggressive, pathologic process. Our study also revealed the association of severe decline and/or certain drop with several potentially 'manageable' determinants like HBa1C, diastolic blood pressure, ~~statin therapy~~, ACE inhibition, other antihypertensive agents and anti-diabetic drugs including insulin therapy. However, some of them may rather be a description of the patients' severe multimorbid condition rather than the cause for a decline in renal function. B~~b~~ecause of its retrospective character, this study is able to formulate hypotheses, but unable to determine any causal relationship. ~~but~~ F~~f~~urther prospective observational and experimental research is needed to clarify the nature of those associations.

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Competing interests: "All authors have completed the ICMJE uniform disclosure form at twww.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work."

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All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: no additional data available

Table 1. Characteristics of the diabetes population in 2010 for all patients, stratified according to the presence or not of CKD.

	All patients			No CKD (62%)			CKD (38%)			
Variable	Obs	Mean/%	SD	Obs	Mean/%	SD	Obs	Mean/%	SD	p
Male	4041	51%		2527	59%		1514	38%		<0.0001
Age	4041	71	11	2527	67	10	1514	77	9	<0.0001
diabetes duration	4041	7.7	6.3	2527	6.6	5.6	1514	9.6	6.9	<0.0001
HbA1c (%)	3128	6.9	1.0	1930	6.9	1,1	1198	6.9	1.0	0.056
HbA1c (mmol/mol)	3128	52	13	1930	52	13	1198	52	13	0.056
MDRD	3260	72	23	1991	85	17	1269	52	17	NA
severe decline	4041	10.4%		2527	7.5%		1514	15.3%		<0.001
% with ≥ 2 certain drop	4041	18.3%		2527	15.8%		1514	22.5%		<0.001
LDL cholesterol	2868	98	33	1823	100	33	1045	95	33	<0.001
SBP	2887	136	14	1848	135	14	1039	136	15	0.224
DBP	2887	79	8	1848	80	8	1039	77	8	<0.001
CVD	4041	29.1%		2527	22%		1514	40%		<0.001
Smoking	1254	14.7%		816	17%		438	10%		0.001
diabetes treatment	4041			2527			1514			
lifestyle only	1510	37.3%		896	35%		614	41%		
OAD	2013	49.8%		1385	55%		628	41%		<0.0001
Insulin	518	12.8%		246	10%		272	18%		<0.0001
antihypertensive	4041	54.5%		2527	51%		1514	60%		<0.0001
ACE inhibitors	4041	44.1%		2527	42%		1514	47%		0.007
platelet inhibition	4041	39.6%		2527	39%		1514	41%		0.145
lipid lowering	4041	48.1%		2527	49%		1514	46%		0.046
Anaemia	3927	3.5%		2472	2.5%		1455	5.2%		<0.001
Osteoporosis	3927	4.2%		2472	2.75%		1455	6.75%		<0.001
psychological distress	3927	11.3%		2472	10.5%		1455	12.7%		0.042
Dementia	3927	1.3%		2472	1.1%		1455	1.7%		0.107
Malignancy	3927	7.1%		2472	5.1%		1455	10.5%		<0.001
Gout	3927	8.0%		2472	6.9%		1455	9.9%		0.001

Table 2. Comparison of kidney-related parameters in patients with CKD, according to the age group.

Age in 2010	40-65 years*		66-80 years		> 80 years	
Variable	N=189/1345 (14%)		N= 765/1842 (41%)		N= 560/854 (66%)	
% with grade 3a -> 5	61%	[54-68]	64%	[60-67]	69%	[65-73]
% with CKD & severe decline	25%	[19-32]	16%	[13-18]	11%	[9-14]
% with CKD & two or more certain drops	27%	[21-34]	26%	[23-29]	16%	[13-20]
Mean MDRD in 2010	56	[54-58]	53	[51-54]	50	[48-51]
Mean CKD duration (yrs)	5.8	[5.3-6.5]	7.8	[7.4-8.1]	9.2	[8.9-9.7]

For dichotomous variables: % and exact (binomial) confidence interval of 95%

For continuous variables: mean value and confidence interval of 95%

Table 3. Logistic regression model analysing the odds of severe decline and its determinants in patients with (N= 1469) and without CKD (N=2385).

	Presence of CKD (N=1469)			**Absence of CKD (N=2385)**		
	Odds Ratio	[95% Conf.	Interval]	Odds Ratio	[95% Conf.	Interval]
age 66-80*	0.55	0.36	0.85	0.85	0.61	1.18
age>80*	0.41	0.25	0.67	1.02	0.63	1.66
Male	1.73	1.25	2.38	1.01	0.74	1.38
HbA1c (%)	1.33	1.13	1.56	1.20	1.05	1.37
Statin****	0.69	0.50	0.96	0.68	0.48	0.95
NCD	2.31	1.96	2.72	1.69	1.43	1.98
DBP (mm Hg)	0.97	0.94	1.00	//	//	//

* reference group age 40-65 years

***Drugs were included in patients' treatment if they had been prescribed for three years or more.

Table 4. Longitudinal logistic regression model with random effect analysing the odds of certain drop and its determinants in patients with CKD (N=1514) and without CKD (N= 3452).

	Patients with CKD (N=1514)			Patients without CKD (N=3452)		
	OR	[95% Conf.	Interval]	OR	[95% Conf.	Interval]
Year	1.10	1.07	1.12	1.18	1.16	1.20
Male	1.20	1.05	1.36	1.02	0.92	1.13
Age group**						
40-65	0.98	0.80	1.20	0.83	0.74	0,93
>80	0.82	0.72	0.95	0.99	0.85	1,16
Diabetes treatment***						
Oral antidiabetics	1.32	1.14	1.52	1.60	1.42	1,79
Additional insulin treatment	1.55	1.29	1.86	1.87	1.55	2,26
ACE inhibitors	1.31	1.14	1.50	1.16	1.03	1.30
Other antihypertensive drugs	1.23	1.07	1.42	1.25	1.12	1.39
Statin therapy	0.86	0.75	0.99	1.42	1.27	1.59
Anaemia	//	//	//	1.76	1.37	2.27
Osteoporosis	//	//	//	1.55	1.21	1.99
Psychological distress	//	//	//	1.27	1.10	1.47

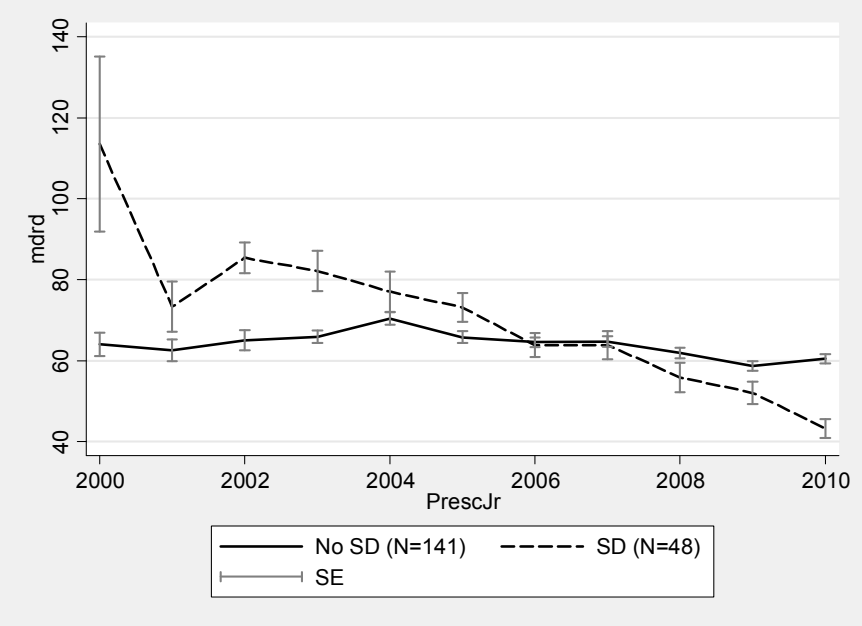
Malignancy	//	//	//	1.35	1.12	1.63

** reference group age 66-80 years

*** reference group: no diabetes drugs

Figure 1. Ten-year evolution of the mean MDRD in patients with diagnosed CKD in 2010 according to the age group and presence or not of significant decline (SD).

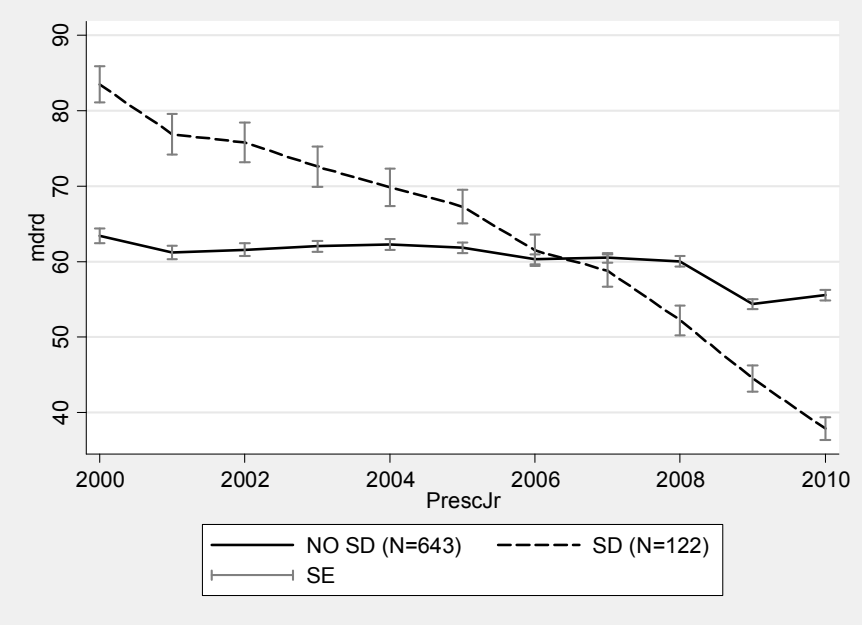
Figura1a. in patients aged between 41 and 65 years in the year 2010.



number of observations at each given year:

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
SD	11	12	20	31	35	57	61	84	98	108	109
No SD	271	329	360	477	545	670	698	757	822	874	983

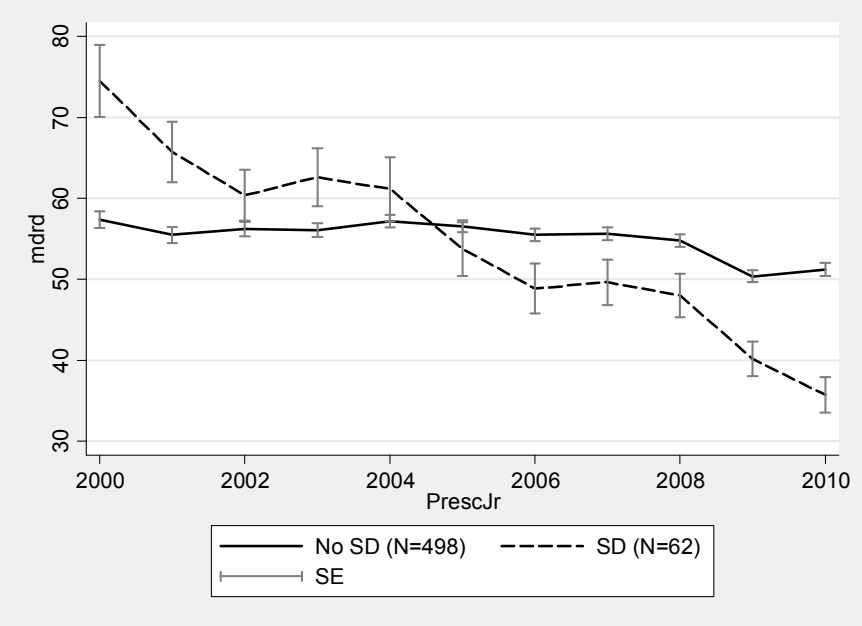
Figure 1b . in patients aged between 66 and 80 years in the year 2010.



Number of observations at each given year:

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
SD	40	41	57	56	72	88	105	117	137	154	148
No SD	628	721	787	937	1030	1166	1224	1272	1291	1360	1398

Figure 1c. In patients aged over 80 in the year 2010.



Number of observations at each given year:

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
SD	29	32	36	33	39	41	45	48	55	56	47
No SD	343	377	418	454	486	541	538	545	570	570	571

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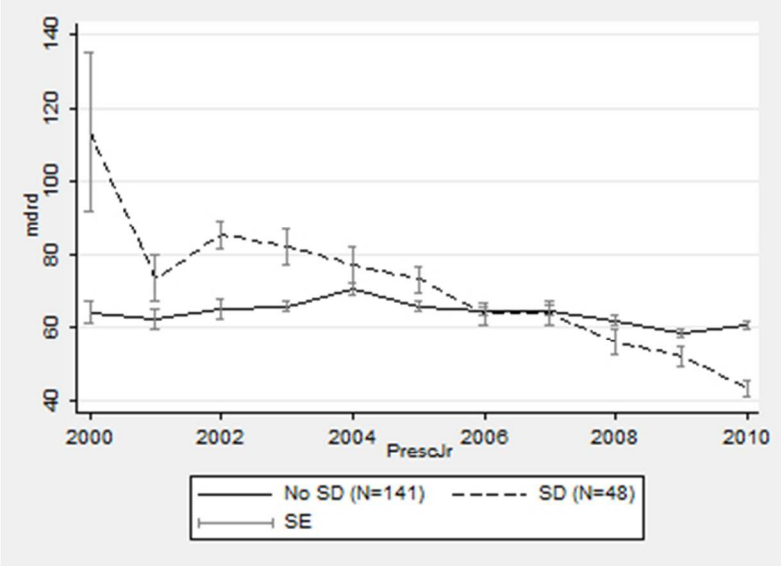

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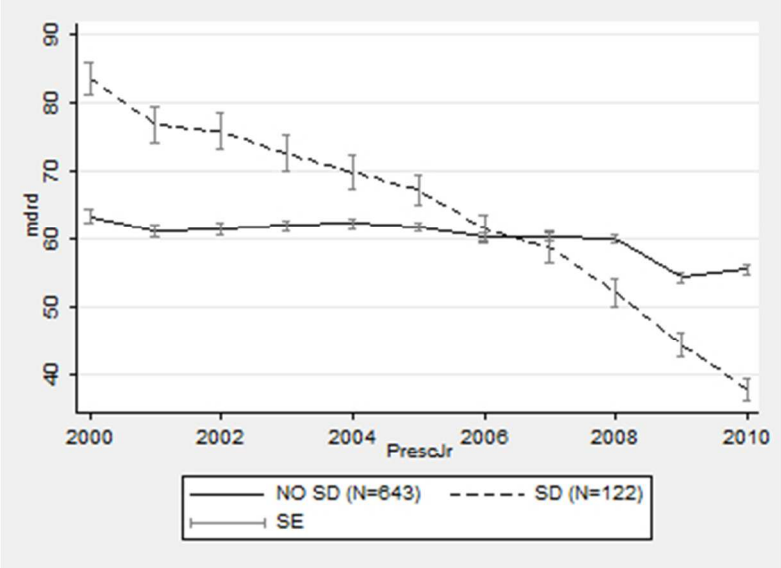

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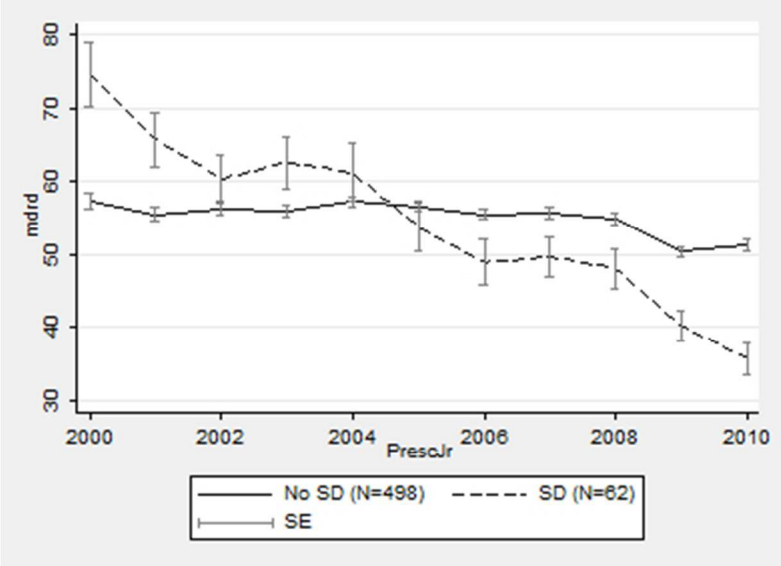

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
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
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
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
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
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
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	8-9

		confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
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	9-10
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	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	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	12

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.