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Incidence rate patterns, cumulative incidences, and time trends for moderate and severe albuminuria in individuals diagnosed with type 1 diabetes under the age of 15 years: a population-based study

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SUMMARY

Background The contemporary incidences of moderate and severe albuminuria and their temporal fluctuations during the past decades are poorly described. Thus, we aimed to assess diabetes duration-specific incidence rates, cumulative incidences, and secular trends of albuminuria in type 1 diabetes.

Methods We conducted a population-based observational study including a random sample (n=1,500) of all individuals diagnosed with type 1 diabetes aged 0-14 years during 1970-99 in Finland. Differences between the calendar-year cohorts 1970-79, 1980-89, and 1990-99 were assessed. Medical records were systematically reviewed for albuminuria determinations.

Findings Between 1970-79 and 1980-89, the cumulative incidence of severe albuminuria had approximately halved (hazard ratio [95% confidence interval] 0·55 [0·42-0·72] with 1970-79 as reference, p<0·001), whereas after this, no further decline was observed (HR 0·83 [0·54-1·26] with 1980-89 as reference, p=0·38). The 25-year cumulative incidences for severe albuminuria were 26·8%, 12·0%, and 10·8% for the 1970-79, 1980-89, and 1990-99 calendar-year diagnosis cohorts, respectively. The progression rate from severe albuminuria to kidney failure was unchanged, as it was 37·5% (28·6-45·2) in the 1970-79 cohort and 36·4% (23·6-47·1) in the 1980-99 cohort 15 years after the onset of severe albuminuria (p=0·37 for difference). Furthermore, the cumulative incidence of moderate albuminuria showed no signs of a calendar effect between 1980-89 and 1990-99 (HR 0·99 [0·78-1·28] with 1980-89 as reference, p=0·97).

Interpretation Our analyses demonstrate that the cumulative incidence of severe albuminuria has decreased between 1970-79 and 1980-99; yet, whether this solely denotes a delay or also a true prevention of albuminuria needs to be explored further. Nevertheless,

diabetic kidney disease remains a significant complication of type 1 diabetes. Due to its robust association with premature mortality, novel therapies to additionally improve the patients' prognosis are needed.

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INTRODUCTION

Despite improved treatment strategies, contemporary analyses project 10 to 12 life-years lost for individuals with type 1 diabetes compared to their diabetes-free sex- and age-matched counterparts.[1] While many factors add to the poor prognosis, a primary driver is the presence and severity of diabetic kidney disease (DKD).[2,3]

DKD is assumed to affect every third individual with type 1 diabetes; yet, it is noteworthy that this understanding mainly stems from studies published 20 to 40 years ago.[4–12] The more recent reports have commonly encountered critical limitations that may have impaired their generalizability, such as single-center study designs, small-scale study cohorts, short observation times, and not following the individuals from the onset of diabetes onwards. Pre-existing incidence studies on moderate albuminuria, the initial clinical manifestation of DKD, are particularly scarce and burdened by the weaknesses. The pre-existing studies are also nearly exclusively confined to individuals diagnosed with diabetes in the 1980s or earlier.

In this population-based study, we sought to present an updated and holistic view of the incidence of DKD with special focus on secular trends. The cohort of 1,500 individuals diagnosed with childhood-onset type 1 diabetes between 1970-99 was followed for up to 50

years. We assessed duration-specific incidence rate patterns and cumulative incidences of moderate and severe albuminuria (formerly termed micro- and macroalbuminuria), as well as progression rates between the stages of DKD. Furthermore, we evaluated the impact of sex and age at diabetes onset on the risk of albuminuria.

METHODS

Study population

The cohort is based on a stratified random sample of 1,500 subjects among all individuals diagnosed with type 1 diabetes before the age of 15 during 1970-99 in Finland. The sampling frame is the database of the Finnish Institute for Health and Welfare compiled from successive cohorts of individuals with childhood-onset type 1 diabetes in Finland, as described earlier.[13] The sampling frame is virtually complete. The sample size was based on power calculation and represents 14.4% of the sampling frame population (n=10,439). The sampling conducted with the SURVEYSELECT procedure in SAS. The calendar-year diagnosis cohorts 1970-79, 1980-89, and 1990-99 are represented to equal extents (500 individuals each), likewise are men and women. The proportion of men in the sampling frame population was 53.9%.

After sampling, altogether 70 individuals were excluded due to characteristics in their clinical course of diabetes not typical of type 1 diabetes, kidney disease other than DKD, insufficient number of AER measurements, or unavailable medical records. Study participants were followed until death, the event of interest (moderate/severe albuminuria or kidney failure), or the most recent event-free date. The attained follow-up time for moderate albuminuria was 20,963 person-years (median [interquartile range; IQR] 21·8 [16·8-27·6] years) and 37,869 person-years (median 25·1 [19·9-32·1] years) for severe albuminuria.

The study was approved by the Finnish Institute for Health and Welfare (THL/786/6·02·00/2016) and Statistics Finland (TK53-26-16). Informed consents were not required due to the register-based study setting.

Diabetic kidney disease

For the ascertainment of the DKD stage, we systematically reviewed the participants' medical records regarding albuminuria measurements. The records were retrieved from diabetes clinic visits until 31 December 2020. We considered both timed 24-hour (10 and 11% of the diagnostic urine samples for moderate and severe albuminuria, respectively), timed overnight (71 and 54%), and spot urine collections (19 and 16%) for the diagnosis of albuminuria. Proportions of the different albuminuria determination methods in the diagnostic urine samples by calendar-year diagnosis cohort appear on **appendix p2**. Following international reference limits, normal AER was defined as <30 mg/24 h or <20 µg/min or an albumin-creatinine ratio (ACR) <3 mg/mmol; moderate albuminuria as AER ≥30 and <300 mg/24 h or ≥20 and <200 µg/min or ACR ≥3 and <30 mg/mmol; and severe albuminuria as AER ≥300 mg/24 h or ≥200 µg/min or ACR ≥30 mg/mmol in two out of three consecutive measurements.[14] The onset of moderate/severe albuminuria was set as the last recorded positive albuminuria measurement in the series of three diagnostic samples. Clinical guidelines recommend against collecting urine samples during urinary tract infections, acute febrile illness, pregnancy, menstruation, severe hyperglycemia, or within 24 hours of strenuous physical exercise. We further checked medical records to exclude any collections that might have been affected by these circumstances. In the absence of albuminuria determinations, we defined severe albuminuria as a 24-hour urinary protein excretion rate >0·5 g or as a positive reading using a reagent strip testing for urinary protein. Altogether 19% of the diagnostic urine samples for severe albuminuria were proteinuria

determinations, ranging from 29% in the 1970-79 cohort to 8% in the 1990-99 cohort (**appendix p2**).

We evaluated the incidence of severe albuminuria in the complete cohort. However, moderate albuminuria was assessed only in the individuals with onset of diabetes in 1980 or later due to the limited accessibility of early albuminuria determinations in those diagnosed formerly. Data on moderate albuminuria were available in altogether 961 individuals, whereas a follow-up status for severe albuminuria was achieved for all 1,430 included study subjects.

Cases of kidney failure, defined as the initiation of maintenance dialysis treatment or having received a kidney transplant, were identified from the Finnish Care Register for Health Care and validated from the medical records.

Statistical analysis

The 1980-89 and 1990-99 calendar-year cohorts of diabetes diagnosis portrayed similar incidence rates and cumulative incidences and were, hence, combined in most of the analyses of the study.

To study duration-specific incidences of moderate and severe albuminuria, the observation time for each study participant was split into multiple observations by half-year duration of diabetes intervals since the diabetes diagnosis using the Lexis macro in SAS.[15] The duration-specific incidence rates were estimated based on the split data. First, patterns of the duration-specific incidences were evaluated by fitting generalized additive models (GAM) to the split data without *a priori* assumptions of the shape of the relation between diabetes duration and the incidence rate.[16] Subsequently, the split data were grouped by five-year intervals, and incidence rates were calculated. Poisson regression models

assessed differences in the duration-specific incidence rates between the 1970-79 and 1980-99 cohorts.

We used the Kaplan-Meier estimator to portray the time-to-event and to calculate cumulative incidences for moderate and severe albuminuria with stratification by the decade of diabetes diagnosis, sex, and age at diabetes onset. Cumulative incidences for kidney failure were defined by the Fine and Gray method, encompassing death as a competing risk.[17]

We used Cox proportional-hazards regression to determine the association between patient characteristics (diabetes diagnosis year, age at diabetes onset, and sex) and the risk of albuminuria. Scaled Schoenfeld residual graphs were visually analyzed to confirm adequacy of the proportional hazards assumption for the diagnosis year cohort, diagnosis age group, and sex. Age at diabetes onset was categorized into three groups: 0-4 years, 5-9 years, and 10-14 years, as the GAM-modeling revealed non-linearity based on the onset age. In these analyses, the calendar-year of diabetes diagnosis was included as a continuous variable.

A two-sided p-value <0·05 was considered statistically significant. Data analysis was performed with R open-source software version 4·1·1 (http://www.r-project.org) and SAS version 9·4 (SAS Institute, Cary, NC, USA).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

The flowchart in **Figure 1** demonstrates the course of DKD in the studied cohort. Among the individuals with diabetes diagnosed in 1980-99, 28·4% (n=273) developed moderate

albuminuria during the observation period. The smoothing plot and absolute incidence rates per five-year intervals of diabetes duration in **Figure 2A** show that the incidence of moderate albuminuria increased until ten years of diabetes duration. Thereafter, the incidence rate remained rather stable until around 25 years of diabetes duration, when it started to slightly decrease. The average incidence rate between 10 and 24 years of diabetes duration was 19·2 (95% confidence interval [CI] 16·5-22·2) per 1,000 person-years.

Altogether 273 individuals (19·1%) developed severe albuminuria. A significant change in the severe-albuminuria incidence rate pattern was observed between 1970-79 and 1980-99 (**Figure 2B**; p for interaction <0·001). In the earlier calendar-year cohort, the incidence peaked at 15-19 years of diabetes (incidence rate 25·8 [19·1-34·1] per 1000 person-years), whereafter it dropped and remained at a lower level throughout the follow-up. However, in the more recent calendar-year cohorts, the incidence rate increase levelled out after 14 years of diabetes. Thereafter, the incidence was on average 10·2 (8·2-12·6) per 1000 person-years and did not decrease during the observation period. The severe-albuminuria incidence rate ratios for the 1980-99 cohort (1970-79 as reference; p-values denote between-group differences) were 0·10 at 5-9 years (p<0·001), 0·35 at 10-14 years (p<0·001), 0·38 at 15-19 years (p<0·001), 0·52 at 20-24 years (p=0·02), 2·27 at 25-29 years (p=0·04), and 1·11 at 30-34 years of diabetes (p=0·85).

After investigating duration-specific incidence rates of moderate and severe albuminuria, we continued to study cumulative incidences of the outcomes. There results, stratified by the calendar-year cohort of diabetes onset, appear in **Figure 3**.

The cumulative incidences of moderate albuminuria increased concomitantly in the two assessed calendar-year cohorts, 1980-89 and 1990-99 (**Figure 3A**). The cumulative incidences were 29·8% (95% CI 25·4-33·9) and 30·7% (24·8-36·2), respectively, after a diabetes duration of 25 years.

Likewise, the cumulative incidences of severe albuminuria were very similar in the two most recent calendar-year diagnosis cohort (**Figure 3B**): 12·0% (9·0-15·0) at 25 years in the 1980-89 cohort and 10·8% (6·7-14·6) in the 1990-99 cohort. However, the cumulative incidence of severe albuminuria was markedly higher in the earliest calendar-year cohort (1970-79), that is, 26·8% (22·6-30·8) after 25 years, 32·6% (28·1-36·9) after 35 years, and 37·8% (32·6-42·6) after 45 years of diabetes.

Finally, the 30-year cumulative incidence of kidney failure (**appendix p3**) was 7·8% (5·6-10·5) in the 1970-79 cohort, while it was 4·2% (2·8-6·0) in the two most recent cohorts (Gray's test p=0·02 for difference).

We further studied progression rates between moderate and severe albuminuria and between severe albuminuria and kidney failure. The cumulative progression rate from moderate to severe albuminuria was 32·2% (95% CI 26·1-37·9) after 5 years and 54·3% (46·0-61·3) after 15 years (**Figure 4A**). **Figure 4B** portrays the cumulative progression from severe albuminuria to kidney failure, incorporating mortality as a competing risk. In the 1970-79 calendar-year cohort, the cumulative progression rate was 37·5% (95% CI 28·6-45·2) 15 years after the onset of severe albuminuria. Of note, the cumulative progression was no different in the 1970-79 cohort compared to the two more recent calendar-year cohorts combined (Gray's test 1970-70 *vs.* 1980-99 p=0·37), the latter group reaching 36·4% (23·6-47·1) 15 years after severe albuminuria had been diagnosed.

Lastly, we evaluated the relationship between albuminuria and age at diabetes onset, sex, as well as diagnosis year as a continuous variable. The GAM-modeling revealed a peak in the risk of severe albuminuria when the age at diabetes onset was between 9 and 10 years (**appendix p4**). When the age at onset was categorized into three groups, the overall lowest risk for moderate and severe albuminuria was seen among the individuals diagnosed with diabetes at an early age (0-4 years; **appendix p5, figures A and B**), whereas the cumulative

incidences in the two other age at onset categories (5-9 and 10-14 years) were no different (log-rank p=0·47 and 0·32 for moderate and severe albuminuria, respectively). Furthermore, neither the risk of moderate nor severe albuminuria was different between women and men when all subjects were combined (**appendix p6, figures C and D**). Yet, as the interaction term between sex and the age at onset categories was significant (p=0·04), we also assessed sex differences within the age at diabetes onset categories separately. The only significant sex difference regarding moderate albuminuria was noted among those with diabetes diagnosis at the age of 10-14 years: in this category, the HR for men compared to women was 1·53 (95% CI 1·04-2·26, p=0·03). The corresponding HRs for men in the 0-4 and 5-9-year age groups were 1·46 (0·83-2·58, p=0·19) and 0·82 (0·56-0·82, p=0·28), respectively. There was no sex-specific difference regarding severe albuminuria among the study subjects with diabetes onset at 0-4 or 5-9 years (HR 1·19 [0·66-2·15], p=0·56 and 0·96 [0·67-1·38], p=0·82, respectively). However, if diabetes had been diagnosed at the age of 10-14 years, the HR for severe albuminuria was 1·75 (1·20-2·55, p=0·004) in men compared to women. **Appendix p6-7, figures E-J** portray the cumulative incidences of moderate and severe albuminuria with stratification for sex and age at diabetes onset.

In a multivariable Cox regression analysis adjusted for all available patient characteristics (**Table 1**), the calendar year of diabetes onset remained significant for severe albuminuria: per one-year increment in the calendar year, the adjusted hazard of severe albuminuria diminished by 5% (95% CI 3-7%). Moreover, onset of diabetes at the age of 5-9 years was associated with an independently higher risk of both moderate and severe albuminuria than the 0-4-year reference group. No additional independent associations were observed.

DISCUSSION

This population-based study revealed secular changes in the diabetes duration-specific incidence rate pattern of severe albuminuria (formerly termed macroalbuminuria) in individuals with childhood-onset type 1 diabetes. A decline in the cumulative incidence of severe albuminuria between the 1970s and the 1980s was also observed, while no further improvement appeared in the 1990s diagnosis cohort. Moreover, the study uncovered that from the onset of recurrent albuminuria screenings until 2020, the cumulative incidence of moderate albuminuria (formerly microalbuminuria) shows no signs of decline. Hence, despite advances in renoprotective treatment, a substantial residual risk of DKD remains.

Some knowledge of the time trends of severe albuminuria in type 1 diabetes has been acquired over the years. In the early 1980s, Krolewski and colleagues from the Joslin Clinic demonstrated an approximately halved risk of persistent proteinuria when comparing individuals with diabetes since the 1930s with individuals with diabetes diagnosed during the two succeeding decades.[4] As reported from the Steno Diabetes Center (previously Steno Memorial Hospital and Hvidöre Hospital) in Denmark, the 25-year cumulative incidence of proteinuria decreased from 41 to 27% between the 1933-42 and 1954-62 diabetes diagnosis cohorts[7], and in a follow-up, the 20-year cumulative incidence of severe albuminuria further fell to 14% in those diagnosed with diabetes in 1979-84.[11] A corresponding decline was observed in Sweden: the 25-year cumulative incidence of severe albuminuria dropped from 30 to 13% between 1961-65 and 1971-75 in the Linköping Diabetes Complications Study.[9]

Nevertheless, not all studies have agreed on a so-called calendar effect for severe albuminuria. In a recent analysis of the Pittsburgh EDC cohort, individuals with onset of type 1 diabetes in 1950-64 and 1965-80 were compared. No difference in the proportion of people with albuminuria was seen between the cohorts, with ~40% of the participants in both cohorts developing severe albuminuria during the first 30 years of diabetes and nearly 60%

during the first 40 years. After 50 years of diabetes duration in the earlier cohort, the cumulative incidence of severe albuminuria had already exceeded 70%.[18]

Yet, contemporary studies of sufficient size to appraise the updated epidemiology of severe albuminuria have been lacking. The dearth of updated knowledge has particularly affected individuals with diabetes diagnosed later than the 1980s.

The current study, encompassing individuals with diabetes diagnosed in the 1970s, 1980s, and 1990s, is the first to have assessed the incidence of albuminuria in type 1 diabetes in Finland – the country with the unenviable distinction of possessing the world's highest incidence of type 1 diabetes.[19,20] The results reveal that the outlook has, indeed, improved when it comes to the burden of severe albuminuria during the first three decades of diabetes. Whereas 27% of those with diabetes since 1970-79 had severe albuminuria 25 years into the disease, the corresponding fraction was only 12% in the 1980-89-cohort; thus, the risk of severe albuminuria had approximately halved between the two decades. Unfortunately, after this, no further progress was seen. The incidence of kidney failure in Finland and its temporal trends has previously been assessed by the Finnish Kidney Register, the most recent analysis of which covered all individuals diagnosed with type 1 diabetes in 1965-2011. A decline in the crude incidence of kidney failure over time was noted, and in agreement with our findings on albuminuria, the difference between the 1965-79 diagnosis cohort and the more recent ones was the most pronounced one.[21]

In the context of diabetes and its long-term complications, the diagnostic tools and therapeutic strategies have taken giant leaps forward during the past 50 years, which undoubtedly contributes to the diminished incidence of DKD. HbA_{1c} was introduced to depict glucose control in the mid-1970s, and blood glucose self-monitoring devices were introduced during the following decade. Moreover, the groundbreaking results of the Diabetes Control and Complications Trial were published in 1993 and led to stricter glycemic

targets in the management of type 1 diabetes.[22] In parallel with this, the understanding of DKD improved: despite that the first immunoassay method to detect urinary albumin was developed in the 1960s, it was not until the early 1980s that the term “microalbuminuria” was coined and recognized as the first step of DKD[23]. Three early landmark studies projected a grim prognosis for individuals with microalbuminuria: during 6-14 years of follow-up, 63-88% progressed to overt kidney disease.[23–25] Even though the study participants with initial microalbuminuria were few, the findings provoked progression to be long considered practically inexorable if albuminuria occurred.

In our cohort, five years after the manifestation of moderate albuminuria, one-third had advanced to severe albuminuria, and this proportion exceeded 50% when 15 years had passed. Although this is substantially lower than what was seen in the seminal studies 40 years ago[23–25], it shows that a considerable risk of progression remains. It is noteworthy that besides our analyses, not many incidence reports on moderate albuminuria in type 1 diabetes exist. In the study with the hitherto longest follow-up, investigating individuals diagnosed with diabetes in 1979-84, the attained cumulative incidence of moderate albuminuria was 34% after a median follow-up of 18 years.[12] Although the two studies are not directly comparable due to disparities in study designs, this incidence rate is somewhat higher than what was noticed in our 1980-99 cohort: after 20 years of follow-up, 23% of the subjects had developed moderate albuminuria, whereas the proportion was 35% after 30 years.

In studies from the 1980s, the occurrence of proteinuria peaked between 10 and 17 years of diabetes[5–7], and one study proposed a second peak after ~30 years[5]. This characteristic natural history has been thought to reflect a genetic predisposition to DKD – if DKD developed exclusively because of cumulative glycemia, the incidence would continue its steady rise until most individuals would be affected.[4] In our cohort, among individuals with

diabetes onset in the 1970s, the occurrence of severe albuminuria peaked after a diabetes duration of 15-19 years, with no second peak to be distinguished. In the two later calendar-year cohorts, the severe albuminuria incidence rate leveled off to a steady rate after an initial 15-year rise. In other words, the characteristic incidence peak had disappeared – a finding analogous to a previous observation from the Pittsburgh EDC cohort.[26] Thus, it seems that modern screening and treatment strategies might be postponing the onset of albuminuria in some of the individuals prone to develop DKD. However, the question of whether we are just delaying or also managing to prevent some cases of DKD is key. At a diabetes duration of 25-29 years, the severe albuminuria incidence rate among those with diabetes onset in 1980-99 was over two-times that of the earlier cohort, which had already passed its incidence peak. On the other hand, the GAM-modeling discovered a reduction of the moderate albuminuria incidence rate after 25 years of diabetes duration, which could suggest that a decline also in the severe albuminuria rate will be attained before the cumulative incidence has reached that of the earlier calendar-year cohort. A re-analysis should be undertaken in the future with longer attained follow-ups in the 1980-99 cohort to assess how large the between-cohort cumulative incidence gap eventually turned out to be.

The GAM-modeling revealed a peak in the risk of severe albuminuria when diabetes had been diagnosed between 9 and 10 years of age. The overall lowest risk was observed in the subjects with diabetes onset before the age of 5, whereas the absolute risk was similar if diabetes had appeared at 5-9 or 10-14 years of age. This phenomenon has been observed by others before[18,21], and hormonal factors have been highlighted as putative underlying culprits. Another plausible explanation is that the adaptation to diabetes management may be more straightforward in individuals with early-onset disease than those with onset around puberty. Whether and how gender influences the DKD risk is not without controversy: while most agree on greater risk among men, others have found no sex difference or even a risk

excess in women.[27] Intriguingly, our study found a male preponderance for moderate and severe albuminuria, although not evident before 20 years of diabetes and exclusively involving those diagnosed with diabetes at 10-14 years of age. If diabetes had appeared earlier, the susceptibility to DKD did not differ between the sexes. Our findings parallel previous observations on kidney failure in Finland (risk excess in men if diabetes had appeared at the age of 10 or later)[21,28] and Sweden (risk excess in men if diabetes had appeared at the age of 20 or later)[29]. A kidney-disease alleviating capacity of estrogen has been theorized[27] – thus, based on our and some previous findings, it could be speculated that the DKD protection in women is solely expressed if it coincides with or occurs later than the pubertal maturation and its concomitant estrogen upsurge. This speculation could serve as a hypothesis for future research within the topic.

The long follow-up dating to modern times, up to 50 years until 2020, is one of our study's main strengths. As the incidences of albuminuria were similar for men and women (*data not shown*), and as the proportions of men and women were virtually equal in the sampling frame population, our estimates are likely representative. Owing to the practically full coverage of type 1 diabetes cases in national registries, we were able to perform a population-based investigation and follow the subjects from the diabetes onset onwards. All Finnish residents are entitled to medical care services in the public health care system, including screening, treatment, and care equipment prescribed in treatment plans. Therefore, the diabetes clinics attended by most individuals with type 1 diabetes are centralized to public health care centers or hospitals, which enabled the acquisition of medical records for over 95% of the original cohort.

However, some limitations should be acknowledged. First, the Finnish populace is characterized by genetic homogeneity and an exceptionally high incidence of type 1 diabetes.[19,20] The prevailing majority of the population is Caucasian. Hence, our results may

not be fully generalizable beyond the Finnish borders. Second, as glomerular filtration rates were unavailable, these results do not portray the whole spectrum of DKD. Third, we cannot rule out the risk that the different albuminuria assessment methods covered and the changes in their representation over time have influenced the results; yet, it is noteworthy that high agreement between 24-hour AER and spot ACR determinations has been established in type 2 diabetes and is therefore surmised in type 1 diabetes as well.[30] Furthermore, although all medical files were reviewed in detail, we cannot fully exclude the risk of false positive albuminuria determinations due to menstruation, preceding strenuous physical activity, or other potentially interfering circumstances. Finally, we report incident cases of moderate and severe albuminuria, but necessarily not persistent ones. As we and others have formerly demonstrated that regression of albuminuria is a recurring phenomenon[31,32], the cumulative incidences do not unequivocally reflect the factual long-term burden of albuminuria.

In conclusion, we present a contemporary and holistic analysis of the burden of DKD due to type 1 diabetes. Our temporal trend analyses reveal that the diabetes duration-specific incidence rate pattern of severe albuminuria has shifted, and the cumulative incidence has significantly dropped. In the combined 1980-99 cohort, 30 and 11% of the individuals developed moderate and severe albuminuria, respectively, during the first 25 years of diabetes, with a plateau phase in the annual incidence rate after an initial rise. Despite that these cumulative incidences are significantly lower than those obtained for the 1970-79 cohort, there is an urge for new therapeutic interventions to improve the patients' prognosis further. Our results also support a male preponderance for DKD; however, only if diabetes occurs in the second decade of life – the underlying reasons of which point towards sex hormones but need further elucidation.

Contributors

FJS and VH designed the study, acquired the data, did the statistical analyses, and verified the underlying data. All authors interpreted the data. FJS wrote the manuscript, and P-HG and VH critically reviewed it. VH had final responsibility for the decision to submit for publication. All authors had access to the data.

Data sharing

The study data will not be available because the General Data Protection Regulation does not allow the distribution of patient-level data.

Declaration of interest

P-HG has received lecture fees from Astellas, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, PeerVoice, Sanofi, and Sciarc. He is an advisory board member for AbbVie, Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Mundipharma, Nestlé, Novartis, Novo Nordisk, and Sanofi. None of these entities participated in the design or interpretation of the study. FJS and VH declare no competing interests.

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FIGURE LEGENDS

Figure 1 A flow chart portraying the development and progression of diabetic kidney disease in the cohort with median (interquartile range) progression times. The numbers in bold font represent the 1970-70 and 1980-99 calendar-year diagnosis cohorts combined. AER, albumin excretion rate; yr, years.

* Of the initial 1980-99 diagnosis cohort, data on moderate albuminuria were available for 961 individuals and on severe albuminuria for 968 individuals.

Figure 2 Diabetes duration-specific incidence rates by five-year intervals and smoothing plots for the relationship between diabetes duration and the incidence of **A** moderate albuminuria (1980-99 cohort) and **B** severe albuminuria. The error bars denote the 95% confidence interval.

* $p<0.05$ for the duration-specific incidence rate in the 1970-79 vs. the 1980-99 cohort

**$p<0.001$ for the duration-specific incidence in the 1970-79 vs. the 1980-99 cohort

Figure 3 Cumulative incidences of **A** moderate and **B** severe albuminuria stratified by the calendar-year cohort of diabetes onset. For severe albuminuria, the HR for the 1990-99 cohort with the 1980-89 as reference was 0·83 (95% CI 0·54-1·26), p=0·38.

Figure 4 The cumulative progression from **A** moderate to severe albuminuria (1980-89 and 1990-99 cohorts combined) and **B** severe albuminuria to kidney failure (for 1970-79 and 1980-99 cohorts

separately). In figure **B**, the competing risk of mortality was accounted for. In figure **B**: purple color, kidney failure; black color, mortality; solid line, 1970-79; dashed line, 1980-99.

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for publications in English until 1 November 2021 using the term “type 1 diabetes” in combination with “albuminuria”, “microalbuminuria”, “macroalbuminuria”, “kidney disease”, or “nephropathy” and “incidence”, “incidence rate”, “incidence rate pattern”, or “cumulative incidence”. We also hand-searched the reference lists of the identified publications to uncover other eligible papers. The search focused particularly on articles reporting the occurrence of albuminuria, its diabetes-duration specific patterns, and its temporal trends in type 1 diabetes.

The inquiry concluded the following: the initial studies within this topic, published in the late 1970s and early 1980s, reported cumulative incidences of proteinuria (corresponding to severe albuminuria) of 30-35% over 25 years and 35-45% over 40 years. In the early studies, a peak in the diabetes duration-specific incidence rate of proteinuria was seen between 10 and 17 years. Some evidence of an incidence decline has emerged after the early studies; however, contrasting results have also been published. Yet, the updated incidence is not fully known, as individuals diagnosed with type 1 diabetes during the 1990s have seldom been represented in the published work. Furthermore, moderate albuminuria has been infrequently assessed.

Added value of this study

This population-based study provides a comprehensive and contemporary picture of the diabetes duration-specific incidence rates, cumulative incidences, and temporal trends of

moderate and severe albuminuria. The study covered individuals diagnosed with diabetes during three consecutive decades, between 1970 and 1999. We did not solely rely on register-based data, as all outcomes (moderate albuminuria, severe albuminuria, kidney failure, and mortality) were verified from medical records. The follow-up extended until 2020.

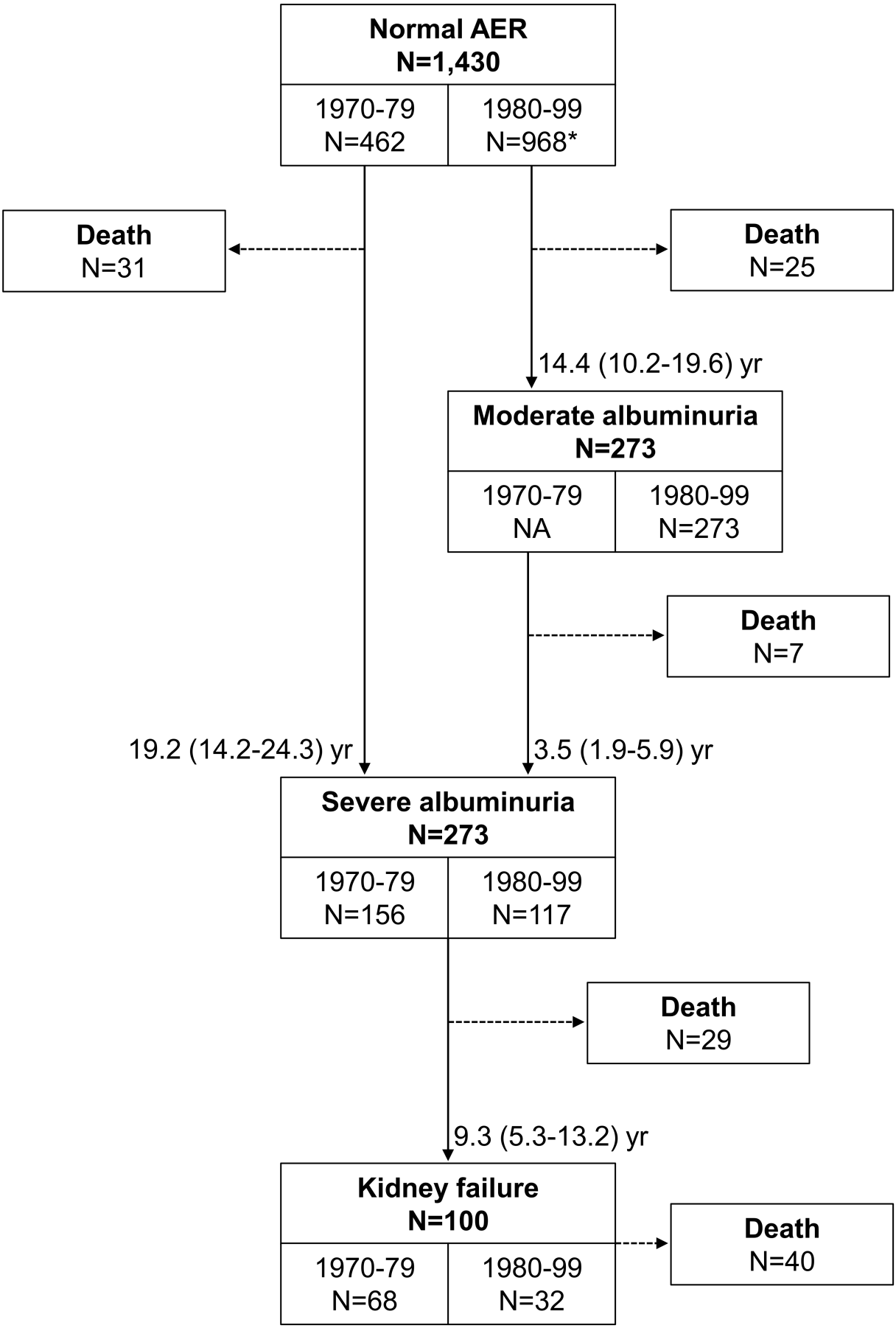
The incidence of moderate albuminuria was assessed among those diagnosed with type 1 diabetes in 1980 or later. The incidence rate of moderate albuminuria rose until ten years of diabetes duration, whereafter it remained stable until 25 years when it started to decline. No difference in the cumulative incidence of moderate albuminuria between those diagnosed with diabetes in the 1980s and the 1990s was observed.

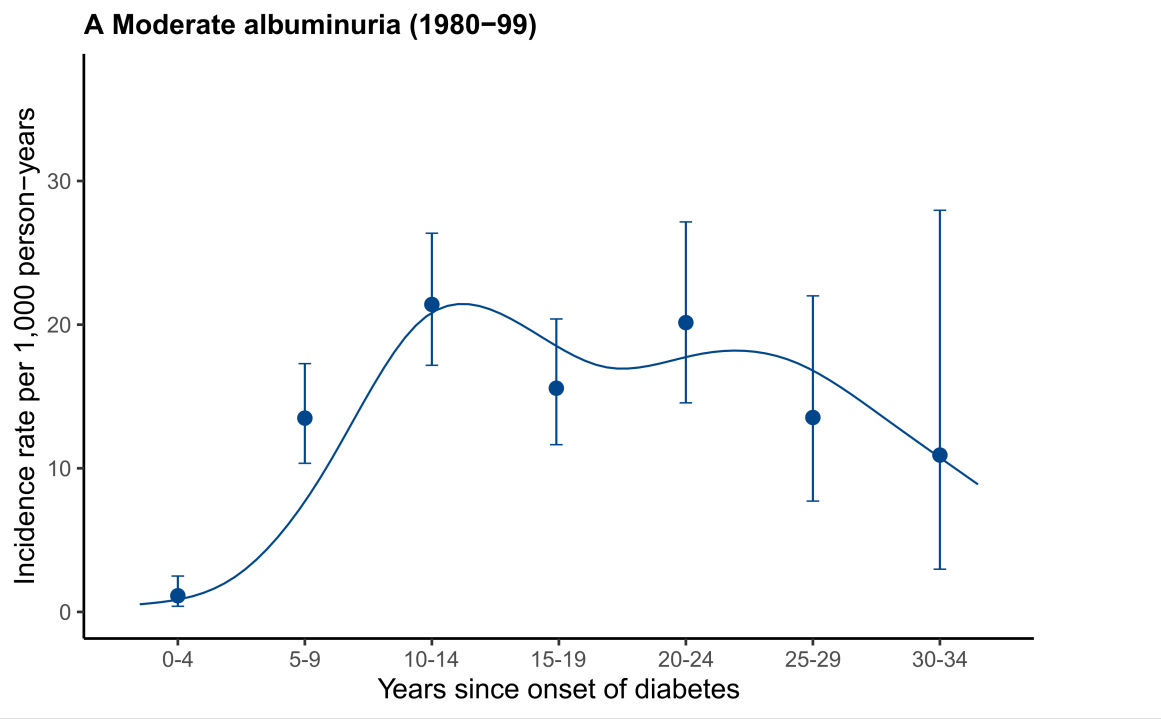
Among the individuals with diabetes onset in the 1970s, a peak in the incidence of severe albuminuria could still be noted between 15 and 19 years of diabetes duration. Yet, after this, the incidence rate pattern had changed; in the combined 1980-99 diagnosis-year cohort, the incidence rate rose up until 14 years of duration, whereafter it levelled off to a plateau and no second incidence rate peak could be distinguished. Between the 1970s and 1980s, the cumulative incidence at 25 years had approximately halved, whereas between the 1980s and 1990s diagnosis-year cohorts, no further drop could be seen. However, the progression rate from severe albuminuria to kidney failure had not changed between the 1970-79 and 1980-99 cohorts.

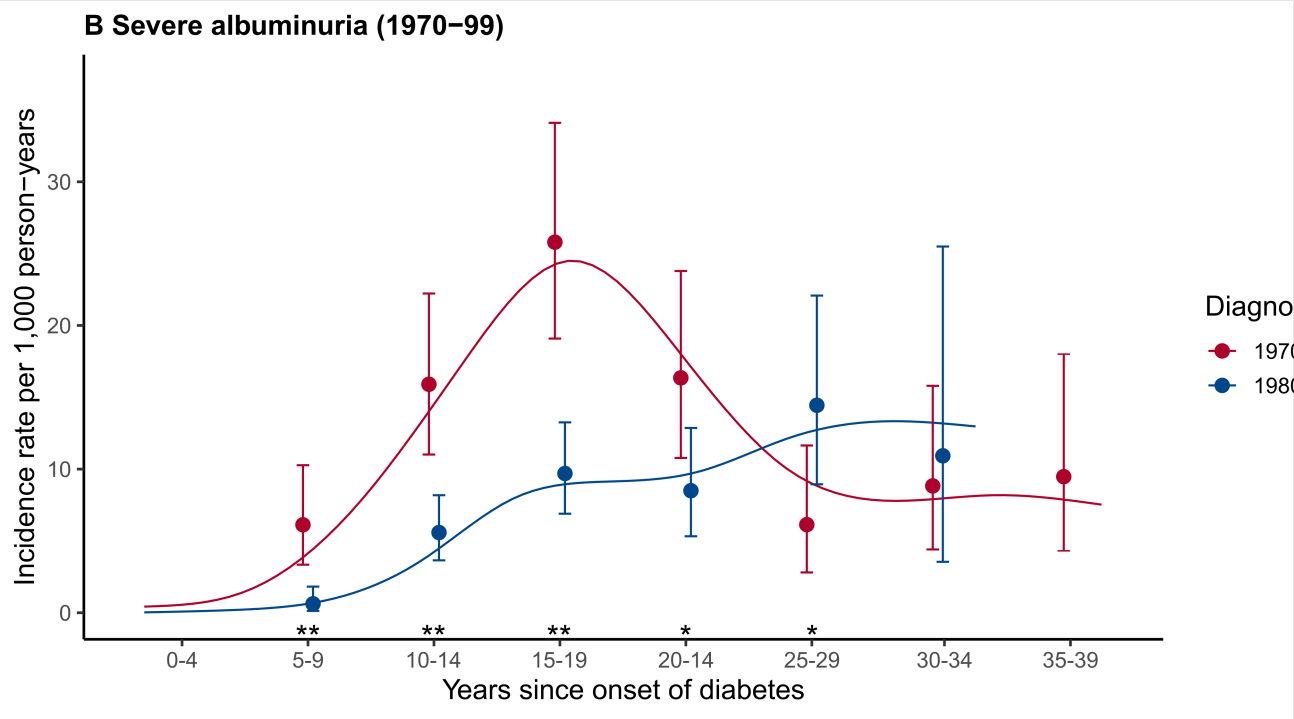
Implications of all the available evidence

Our study together with previous publications within the field have demonstrated that severe albuminuria has burdened approximately every third individual diagnosed with type 1 diabetes in the 1970s and prior to that. After this, most likely owing to the vast advances in diabetes and kidney disease therapy, the cumulative incidence has dropped significantly. However, no further progress was observed between the 1980s and 1990s calendar-year

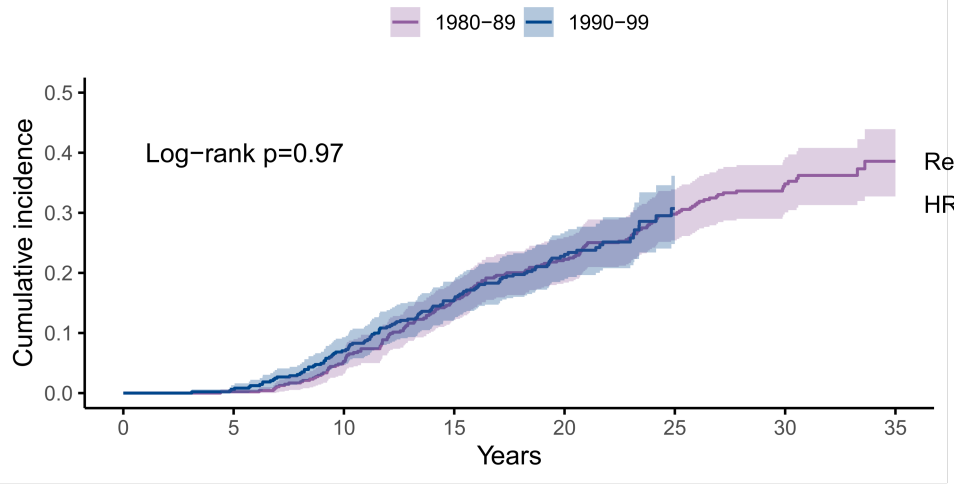
diagnosis cohorts. Therefore, a need for new therapeutical interventions to further diminish the residual diabetic kidney disease risk persists.


Normal AER
N=1,430
1970-79
N=462
1980-99
N=968*
Death
N=31
Death
N=25
14.4 (10.2-19.6) yr
Moderate albuminuria
N=273
1970-79
NA
1980-99
N=273
Death
N=7
19.2 (14.2-24.3) yr
3.5 (1.9-5.9) yr
Severe albuminuria
N=273
1970-79
N=156
1980-99
N=117
Death
N=29
9.3 (5.3-13.2) yr
Kidney failure
N=100
1970-79
N=68
1980-99
N=32
Death
N=40


A Moderate albuminuria (1980−99)
Incidence rate per 1,000 person−years
0
10
20
30
0-4
5-9
10-14
15-19
20-24
25-29
30-34
Years since onset of diabetes


B Severe albuminuria (1970−99)
Incidence rate per 1,000 person−years
0
10
20
30
**
**
**
*
*
0-4
5-9
10-14
15-19
20-14
25-29
30-34
35-39
Years since onset of diabetes
Diagnosis cohort
1970-79
1980-90

A Moderate albuminuria



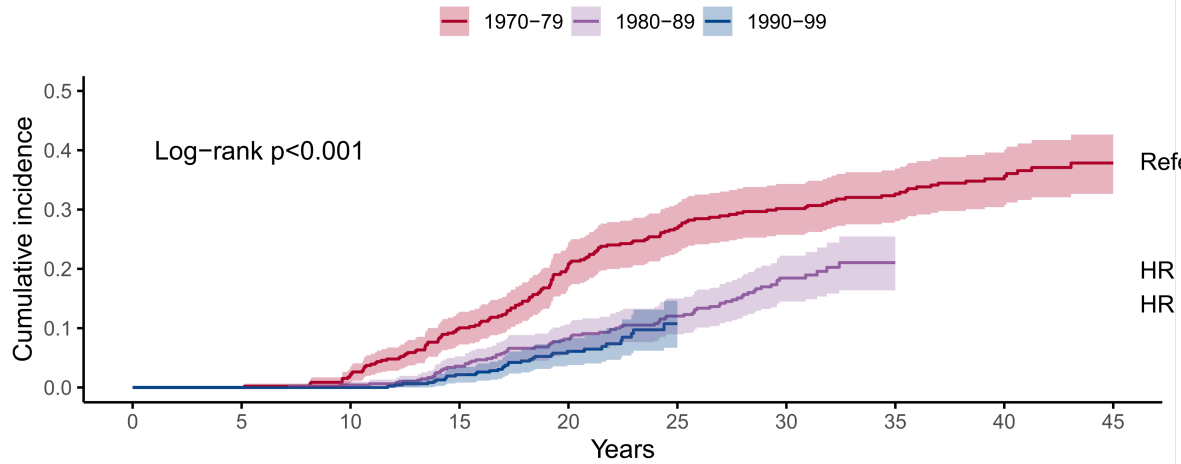
Reference

HR 0.99 (95% CI 0.78-1.28)

No. at risk

475	474	449	395	344	270	161	29
486	483	445	378	245	58	0	0

B Severe albuminuria



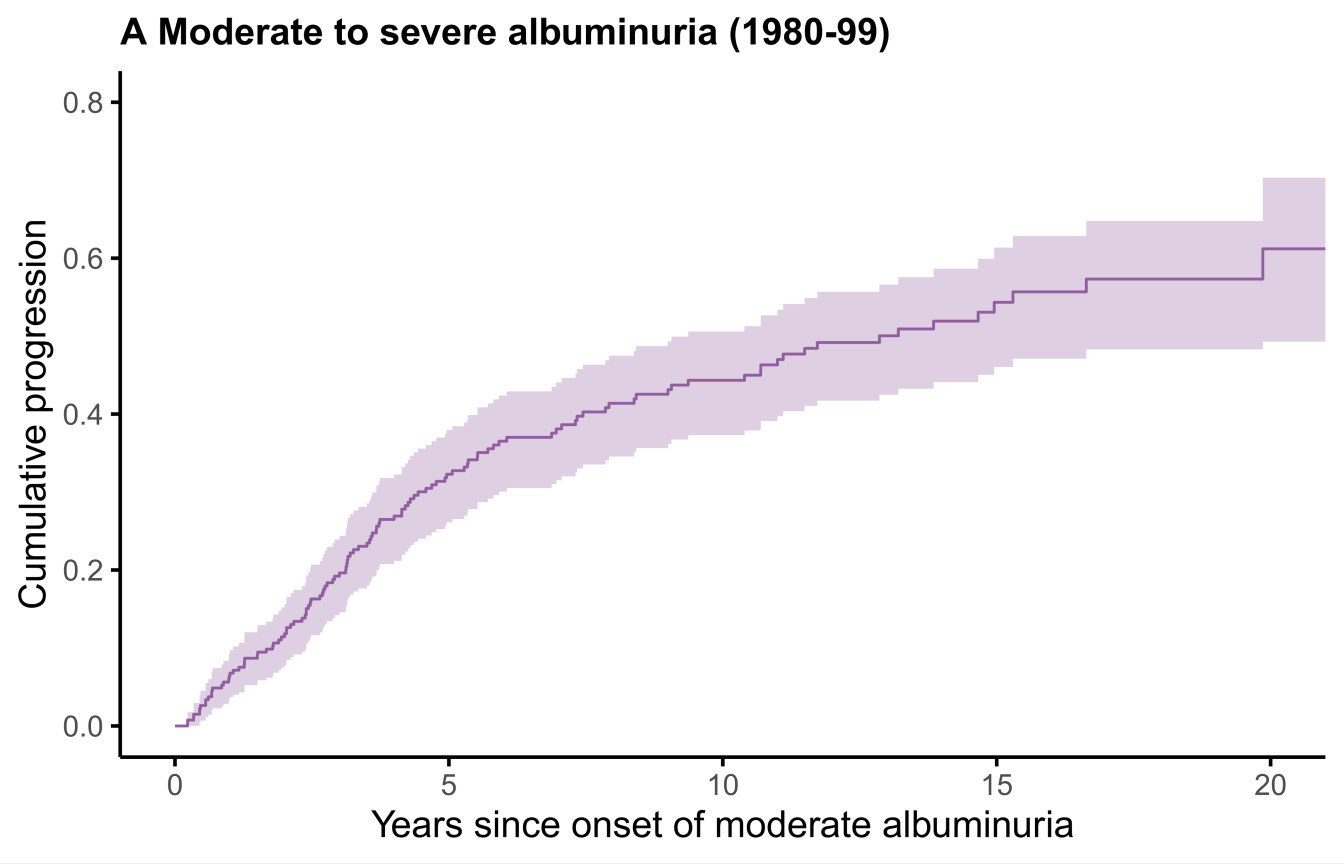
Reference

HR 0.55 (95% CI 0.42-0.72), p<0.001

HR 0.36 (95% CI 0.25-0.53), p<0.001

No. at risk

462	462	448	405	352	311	279	229	145	43
481	481	478	453	408	338	202	40	0	0
487	487	481	442	302	71	0	0	0	0


A Moderate to severe albuminuria (1980-99)
Cumulative progression
0.0
0.2
0.4
0.6
0.8
0
5
10
15
20
Years since onset of moderate albuminuria

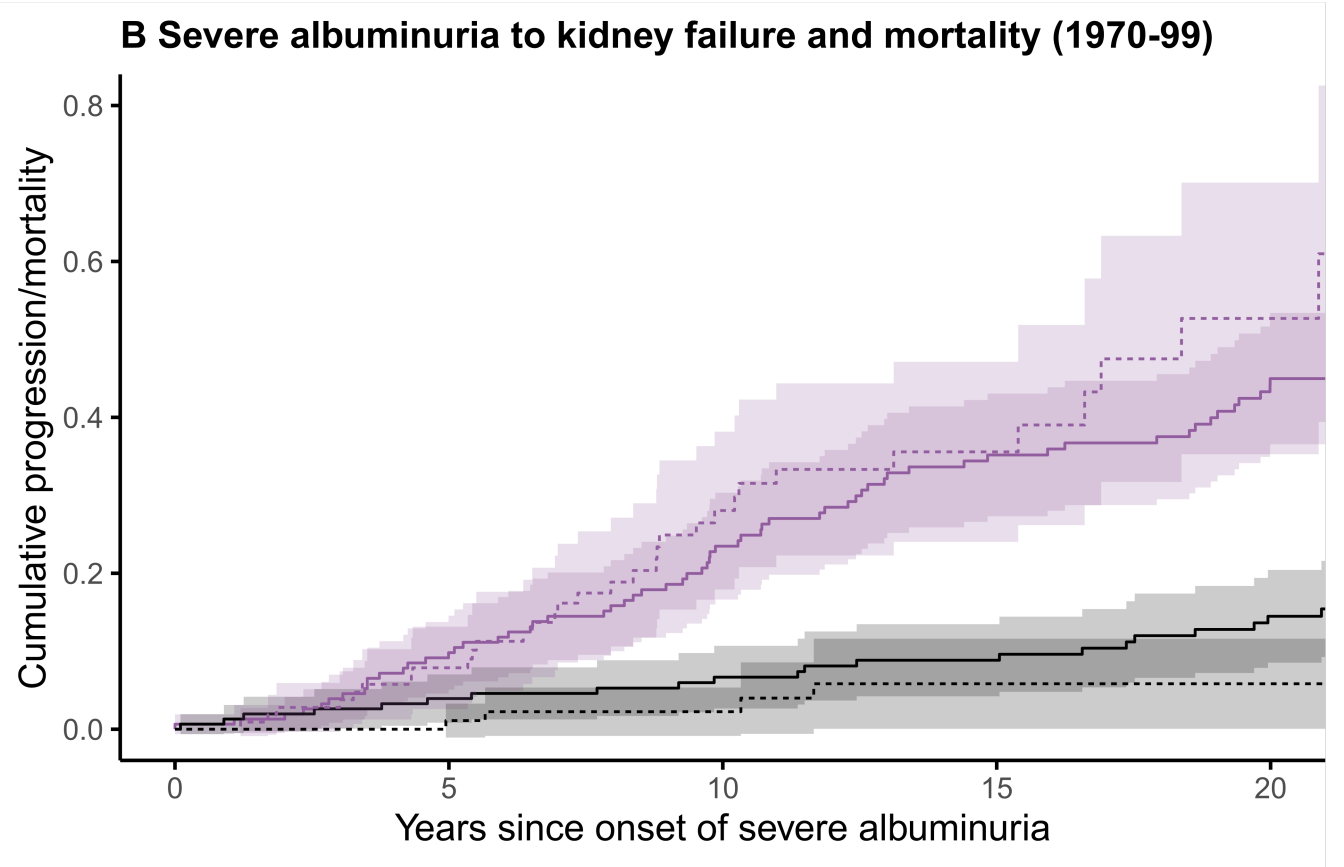

B Severe albuminuria to kidney failure and mortality (1970-99)
Cumulative progression/mortality
0.0
0.2
0.4
0.6
0.8
0
5
10
15
20
Years since onset of severe albuminuria

Table 1 Results from Cox proportional-hazards regression analyses evaluating the associations between patient characteristics and the hazard of albuminuria.

	Moderate albuminuria		Severe albuminuria	
Individuals	*n=961*		*n=1,430*	
Events	*n=273*		*n=273*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Diagnosis year	0.99 (0.96-1.01)	0.21	0.95 (0.93-0.97)	<0.001
Age at diabetes onset				
0-4 years	Reference		Reference	
5-9 years	1.60 (1.14-2.23)	0.006	1.48 (1.05-2.09)	0.03
10-14 years	1.38 (0.98-19.3)	0.07	1.32 (0.93-1.86)	0.12
Sex				
Women	Reference		Reference	
Men	0.99 (0.96-1.01)	0.25	1.27 (1.00-1.61)	0.05