Incidence Trends and Predictors of Hospitalization for Hypoglycemia in 17,230 Adult Patients With Type 1 Diabetes: A Danish Register Linkage Cohort Study

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OBJECTIVE

This study aimed to examine nationwide incidence trends and predictors of hospitalization for hypoglycemia (HH) in the adult population with type 1 diabetes in Denmark.

RESEARCH DESIGN AND METHODS

All 17,230 patients with type 1 diabetes aged 16 years and above registered in the Danish Adult Diabetes Database (DADD) from 2006 were followed to 2012 by linkage of registers. Incidence rates of HH were modeled by Poisson regression by calendar time, taking sex, age, diabetes duration, clinical variables, and previous HH into account.

RESULTS

A total of 2,369 events of HH occurred among 1,735 patients with type 1 diabetes of HH during 70,002 patient-years (mean follow-up 3.7 years). A decrease in incidence rate was observed with calendar time with an 8.4% (4.9–11.7%) annual decrease. Predictors of HH included previous HH, age, diabetes duration, albuminuria, and HbA_{1c}.

CONCLUSIONS

This study revealed a decreasing trend in incidence of HH in patients with type 1 diabetes. Previous HH, longer diabetes duration, macroalbuminuria, and HbA_{1c} were associated with increased risk of HH in type 1 diabetes, and attention to those factors is warranted in both clinical and public health aspects.

Hypoglycemia is considered a major challenge to glucose-lowering therapy among patients with type 1 diabetes, with 90% of all patients who receive insulin experiencing hypoglycemia (1). Hypoglycemia can range from asymptomatic episodes that remain unrecognized by the patient to mild symptomatic events managed by the patient alone and severe hypoglycemia with cognitive disruption and need for assistance from others. Ultimately, severe hypoglycemic episodes may require hospital treatment as a result of severity or lack of treatment options in the surroundings. Such episodes are feared by patients and relatives and generate considerable societal costs.

Numerous studies have measured the incidence rate of hypoglycemia and severe hypoglycemia in type 1 diabetes, but results have varied considerably depending on

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the definition of hypoglycemia, group selection (whether high-risk patients were included or not), and the type of study (2). Over the last decades, insulin treatment has changed with increased use of analog insulin, insulin pump treatment, and continuous glucose monitoring (3). However, it is not clear to what extent recent advances in type 1 diabetes care has reduced the incidence of severe hypoglycemia, and we are not aware of any study that examined the recent trends in hospitalization for hypoglycemia (HH) incidence in adults and older patients with type 1 diabetes in a large sample. This study aims to describe the time trends in HH in adults and older patients with type 1 diabetes in Denmark from 2006 to 2012 and to investigate predictors of incident HH.

RESEARCH DESIGN AND METHODS

Study Population and Registries

The study base comprised all patients diagnosed with type 1 diabetes aged 16 years and older who have been registered in the Danish Adult Diabetes Database (DADD) during 2006 to the end of 2011. In total, data from 23,268 patients were extracted from the DADD register. DADD is a nationwide clinical register, established in 2005, operated and financed by the Danish Regions (4). The aim of this register is to monitor the quality of diabetes care in Denmark. Hospital outpatient clinics and general practitioners are obliged to report annual clinical data for all patients with diabetes aged ≥16 years, including information on date of birth, sex, weight, height, smoking, date of diabetes diagnosis, HbA_{1c}, blood pressure, antihypertensive drug use, dyslipidemia drug use, urinary albumin-to-creatinine ratio (ACR), and status date (the date of clinical information updated/reported in DADD). The data completeness in DADD has been estimated to be >95%. The DADD data were linked to the following registries using the unique personal identification number for all people in Denmark: *1*) the Danish Register of Causes of Death (information on cause of death and date of death available since 1970 covering all deaths in Denmark) and *2*) the Danish National Patient Register (all somatic hospital admissions since 1977, including information on HH). Since 1995, data on outpatients and emergency contacts are also included.

Diagnostic Criteria

The diagnosis of type 1 diabetes in DADD is based on the clinical definition according to national guidelines provided by the reporting specialist clinic. HH was defined as the ICD-10 codes E100, E110, E120, E130, E140, and E162; this wide range of code for HH was considered to ensure coverage of all HH events. However, the codes E100 and E120 made up the largest part of HH diagnoses (87% and 7%).

Measures of Exposures

Baseline characteristics were derived from DADD and measured based upon the patients' date of entry in DADD, as shown in Table 1. BMI was categorized as underweight (<18.50 kg/m^2), normal weight (≥18.50 to ≤24.99 kg/m^2), overweight (≥25 to ≤29.99 kg/m^2), and obese (≥30 kg/m^2) adapted from the World Health Organization; albuminuria (ACR) was stratified into normoalbuminuria (<3 mg/mmol), microalbuminuria (3 to ≤30 mg/mmol), and macroalbuminuria (>30 mg/mmol); smoking was characterized into never smoker, ex-smoker, occasional smoker, and daily smoker; dichotomous variables were sex (male or female), antihypertensive drug use (yes or no), and lipid-lowering treatment (yes or no). Age (age measured at entry), age at diabetes onset (years), diabetes duration (years), HbA_{1c} (%/mmol/mol), and systolic blood pressure (mmHg) were included as continuous variables.

Measurement of Outcome

HH was defined as an event when it required an outpatient, inpatient, or emergency care visit with the previously mentioned corresponding diagnostic code to ICD-10 code for HH.

Follow-up

All patients with type 1 diabetes in DADD were followed from or earliest status date in DADD (May 2005 and onward) prospectively to the end of 2011 or death, whichever came first. We excluded episodes of HH that followed <1 week after a previous event, as these are considered to be double registrations. A group of patients had their first entry in DADD by 31 December 2011 and were excluded as their follow-up period was estimated to be <1 day. In addition, due to erroneous coding, individuals aged <16 years old at entry in DADD, diabetes duration longer than age, BMI <10 or >100, or HbA_{1c} <0 were also excluded (total n = 1,455). Finally, 17,320 individuals (9,873 men and 7,357 women) were included in the study.

Statistical Analysis

The follow-up of patients was subdivided at the dates of recorded HH, and the number of HH events prior to entry of each patient were counted, enabling us to classify each interval of follow-up by the number of previously seen HH events (0, 1,. . .5) (Supplementary Fig. 1). Each follow-up interval thus ended at death, next HH, or censoring (at the end of the study period). Finally, follow-up intervals were subdivided in 3-month intervals along the calendar timescale. For each interval we could then compute the current age, current date, current duration of diabetes, and, for follow-up of people with at least one prior HH, the time since last HH event, thus rendering four different timescales. HH occurrence rates were modeled in a multistate model by Poisson regression using the event indicator (next HH) as outcome and the log person-years as offset. The same person may contribute several events, but because we are modeling these as separate types of event (with different rates), different events within the same individual contribute to the underlying likelihood as were they independent Poisson observations. Mortality rates were not modeled.

We modeled the HH occurrence rates by cubic splines (three parameters each) for the four timescales, including an interaction between number of previous HH events and time since last HH event, by sex, smoking status, and use of antihypertensive medication and lipid-lowering medication and by linear terms of the clinical variables HbA_{1c}, BMI, and systolic blood pressure. Because a substantial fraction of patients had missing values of albumin, the albumin effect (using the log10 transform of it) was estimated in a secondary (presented) analysis, including albumin in addition to the other variables. We tested for nonlinearity of all included continuous variables by including a quadratic term and using likelihood ratio tests. A full description of the analysis can be seen at http://bendixcarstensen.com/SDC/KZIA/HH-DK.pdf.

Ethical Consideration

Register-based studies do not require ethical approval in Denmark. The Danish Data Protection Agency approved both the access and the use of the described data in this study (2007-58-0015, SDC-2013-003, serial number 02090).

Table 1—Baseline characteristics of patients with type 1 diabetes (*n* = 17,230) in the DADD: *n* and % for categorical variables and percentiles (P) of continuous variables

Characteristics	*n*	%
Population	17,230	100.0
Sex		
Male	9,873	57.3
Female	7,357	42.7
BMI, (kg/m^2)		
Underweight	1,051	6.1
Normal weight	7,967	46.2
Overweight	6,035	35.0
Obese	2,177	12.6
Urinary ACR		
Normoalbuminuria (<3)	10,475	60.8
Microalbuminuria (3 to ≤30)	400	2.3
Macroalbuminuria (>30)	41	0.2
No information	6,314	36.6
Smoking		
Never smoker	6,808	39.5
Ex-smoker	2,313	13.4
Occasional smoker	629	3.7
Daily smoker	5,248	30.5
No information	2,232	13.0
No. of past HH		
No event	13,010	75.5
1 event	2,562	14.9
2 events	900	5.2
3 events	436	2.5
4 events	204	1.2
>4 events	118	0.7
Antihypertensive drug use		
No	10,968	63.7
Yes	6,262	36.3
Dyslipidemia drug use		
No	11,464	66.5
Yes	5,766	33.5

Characteristics	P_{5th}	P_{25th}	P_{50th}	P_{75th}	P_{95th}
Date	03/2006	02/2007	06/2007	02/2009	02/2011
Person-year	0.6	2.2	4.1	4.8	5.7
Age (years)	20.0	34.1	45.6	57.7	71.7
BMI (kg/m^2)	19.7	22.6	24.8	27.5	33.1
Diabetes duration (years)	0.7	7.2	16.3	28.3	45.6
HbA_{1c} (mmol/mol)	44	55	64	74	96
Systolic blood pressure (mmHg)	108	120	130	141	165
Urinary ACR	0.0	0.5	1.0	2.3	22.8

RESULTS

A total of 18,285 patients, of whom 42.8% (7,821) were female, contributed a total of 70,002 patient-years during the follow-up period of May 2005 to the end of 2011. The analysis was based on 17,230 patients with all clinical variables known and follow-up to the sixth HH; 65,476 patient-years and a total of 2,369 events of HH among 1,735 patients. Before December 2011, 3.5% (609 patients) died.

Baseline characteristics are presented in Table 1 for 17,230 patients with clinical information. Median age at entry was 45.6 years, the median diabetes duration was 16.3 years, and median HbA_{1c} in the patient population was 64 mmol/mol. Almost half of the population was overweight, one-third were daily smokers, and one-third were treated with lipid-lowering or antihypertensive drugs. Twenty-five percent had one or more previous HH events at entry. In addition, a nonsignificant increase in mean HbA_{1c} was observed from 2006 to 2012.

HH Incidence Trends

The overall crude incidence of HH during follow-up was 3.38 per 100 patient-years and decreased from 2006 to 2012. Total number of HH events and crude incidence rates according to calendar year and sex are presented in Table 2. There was a steady decline in crude incidence rates over the 7 years of follow-up, with a reduction from 2005 at 5.1 per 100 patient-years to 2.8 per 100 patient-years in 2011. We found no evidence of nonlinear time trends with HH (P = 0.826), and a linear model of calendar time showed an annual decrease in HH of 8.4% (4.9–11.7%), confirming the initially observed time trends. Predicted rates of first HH occurrence excluding those with previous HH at entry are shown in Supplementary Fig. 2 as a function of age for the years 2006 and 2011, and approximate median values of all other variables in the model.

Risk Factors for HH

There was a strong nonlinear effect of age on HH with a rate ratio of ~1.6 for patients at age 20 and 80 years compared with middle-aged patients (Fig. 1*B*). We found a modest but clear increase in HH incidence with increasing diabetes duration (Fig. 1*C*). Previous HH was strongly associated with HH with more than threefold increased risk of HH for patients with four previous events of HH compared with patients with no events, gradually lower with fewer previous events (Fig. 1*D*). Furthermore, the highest relative risk was observed within the first years after the last HH event. We found no interaction between time since last HH and number of previous HHs (P = 0.239); thus we report estimates from a model with a (log-) linear effect of calendar time and proportional hazards along the time since HH event between different number of previous HH events.

HbA_{1c} and albuminuria were significantly associated with incident HH ($P < 0.05$), but sex, BMI, smoking, and antihypertensive and lipid-lowering

Table 2—Crude incidence rates of HH (per 100 patient-years) in patients with type 1 diabetes during 2006–2012

Calendar year	No. of HH cases	Patient-years/1,000	Incidence rate (in all patients) with 95% CI
2006	92	1.8	4.5 (3.9–5.2)
2007	335	8.6	4.0 (3.7–4.3)
2008	453	12.4	3. 6 (3.3–3.9)
2009	478	14.4	3.4 (3.2–3.6)
2010	512	15.6	3.2 (3.0–3.5)
2011	494	17.1	2.8 (2.6–3.1)

treatment were not significantly associated with HH (Table 3). The association with HbA_{1c} was nonlinear, with a marked increase in HH risk at HbA_{1c} >60 mmol/mol (Fig. 1*A*). Categorization into macro-, micro-, and normoalbuminuria showed similar associations (hazard ratio [HR] 1.98 [95% CI 1.21–3.22] and HR 1.49 [95% CI 1.22–1.84] vs. normoalbuminuria).

CONCLUSIONS

This longitudinal study provides the most recent data on time trends in HH, with information available until 2012. The study shows a steady decline of HH incidence rates during 2006–2012 in patients with type 1 diabetes in Denmark. The incidence rates observed were remarkably low compared with previous studies in patients with type 1 diabetes (5–8). This study also reports a number of risk factors of HH, including past history of HH, albuminuria, long diabetes duration, and high HbA_{1c} in adults with type 1 diabetes.

Incidence Rates and Trends of HH

A novel finding of our study was the remarkably low rates of HH observed in patients with type 1 diabetes with a steady decline from 2006 to 2012. Moreover, this decrease in incidence rates was observed in the fully adjusted model. These low rates of incidence of HH are comparable with a recent study in the U.S. where the rate for an emergency department visit due to hypoglycemia reported was 1.8 in 2006 and 1.4 in 2011 per 100 patient-years; however, the study was unable to classify diabetes into type 1 and type 2 (5). Another recent U.S. study in a large group of patients with diabetes reported incidence rates of any hypoglycemia-related emergency care visits or inpatient encounter in the range of 1.4–1.6 per 100 patient-years during 2005–2011 (6). Nevertheless, other studies that estimated high incidence rates of HH differ from our study in several aspects. A Scottish study that reported a rate of 11.5% per year in patients with type 1 diabetes in the study period from 1997 to 1998 (7) defined hypoglycemia as an episode that required emergency treatment from primary care, ambulance, accident, emergency, or hospital services. Another study in Minnesota reported that 18% of patients with type 1 diabetes were admitted to the hospital due to hypoglycemia during 7 years of follow-up. In this study, hypoglycemia was defined as any ambulance calls and emergency medical services due to hypoglycemia in patients with type 1 diabetes (8). Most patients in the cohort of Minnesota were treated with multiple daily insulin injections and had a high degree of comorbidities. This may explain the high rate together with the broad definition of hypoglycemia (8). The steep decline in HH with calendar time in our study is in line with some recent studies; Wang et al. (5) in their nationwide study in the U.S. observed decreasing trends of emergency department visits due to hypoglycemia for all age and sex groups. Another recent U.S. study observed decreasing trends of HH in all age and sex groups in older Medicare beneficiaries all over the U.S. (9). However, none of these studies were able to scrutinize incidence trends of HH in adult patients with type 1 diabetes.

These encouraging findings are most likely due to several improvements in diabetes care. Changes in clinical practice by the implementation of the American Diabetes Association/International Society for Pediatric and Adolescent Diabetes guidelines in 2007 with glycemic target settings (HbA_{1c} 7.5% [58 mmol/mol]) and widespread use of analog insulin, improved diabetes education, and frequent use of insulin pumps with or without continuous glucose monitoring in recent years may have contributed to this improvement in severe hypoglycemia control in Denmark (10–12). Furthermore, it is relevant to mention that as part of the improvement in diabetes complication treatment, it is likely that more cases of severe hypoglycemia are now treated at home with glucagon injection by acute ambulance services or by educated family members. Finally, the reduction of HH observed during 2011 and 2012 may be explained by increased family treatment as a consequence of the implementation of stricter new EU driver licensing regulations disqualifying patients with recurrent severe hypoglycemia from maintaining their license (13). Unfortunately, no register information on prehospital treatment is available in Denmark.

Risk Factors of HH

Like most of the existing studies, we also found that previous HH was a strong predictor of HH in this patient group (14–16). Risk of HH was increased by ~3 times, 2.6 times, ~2 times, and 1.6 times, respectively, in the patient groups with four or more events, three events, two events, and one episode of HH before study entry compared with those who had no event. None of the earlier studies examined past experience of HH similarly (14–16). Previous HH may be a marker of several risk factors, including impaired hypoglycemia awareness and poor self-care or lack of family support during daily life. Further studies are needed to understand this mechanism.

Longer diabetes duration was identified as a risk marker for HH in our analyses. This finding is consistent with several other large studies (7,15) and may be driven by a growing proportion of subjects with impaired hypoglycemia awareness with increasing diabetes duration. Development of complications in the natural progression of diabetes at a later stage could increase the risk of HH in patients with type 1 diabetes (17), supported by the fact that albuminuria was also associated with increased risk of HH. However, the current study could not adjust for patient's comorbidity status, especially long-term diabetes complications and hypoglycemia unawareness, which needs to be taken into account when interpreting our results.

In contrast to previous large studies, including the Diabetes Control and

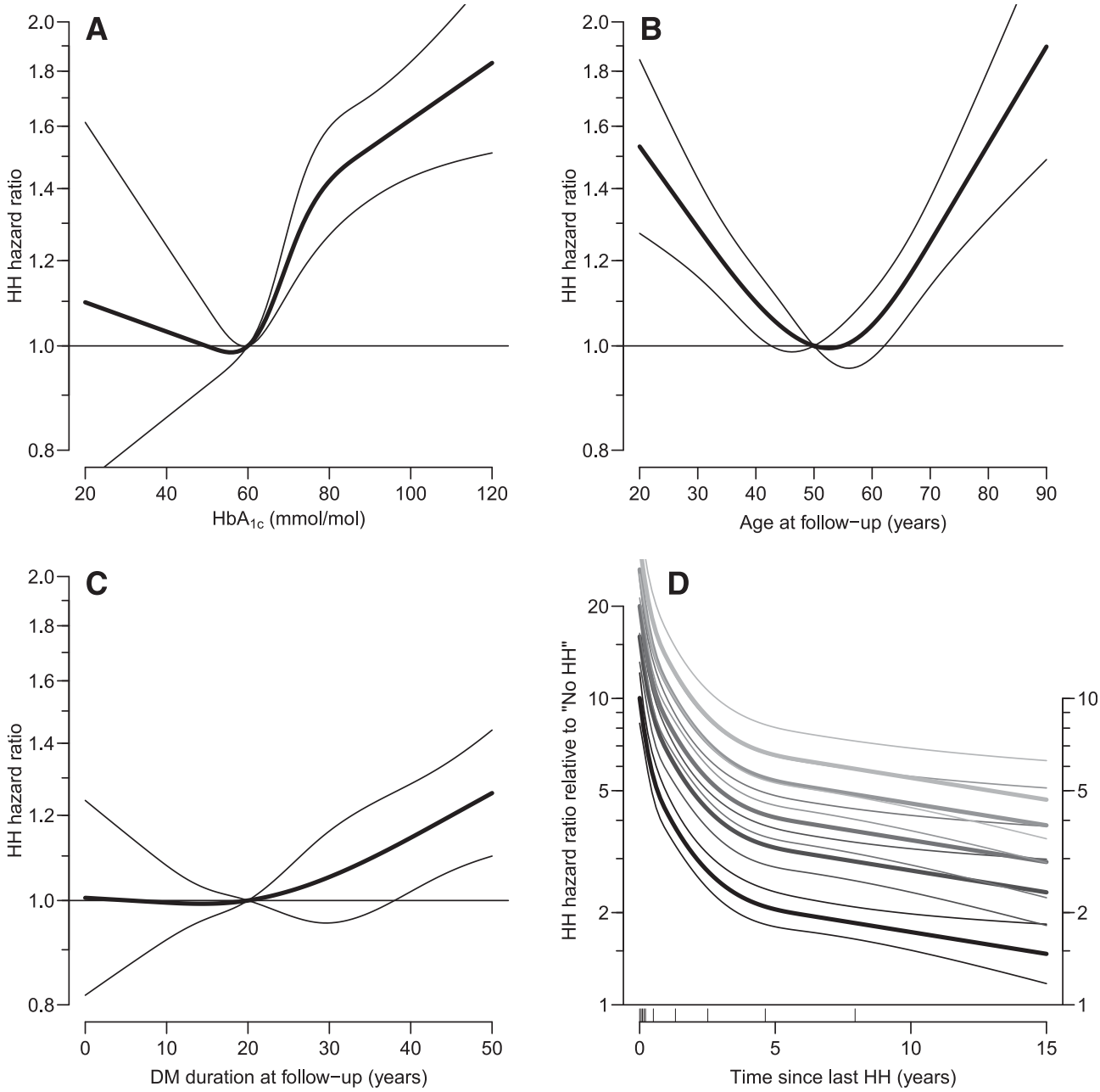

Figure 1—Estimated time effects on HH from a model with a linear effect of calendar time and proportional effects of time since previous HH according to HbA_{1c} (*A*), age (*B*), diabetes duration (*C*), and time since last HH (*D*). Panel *D* shows the HR relative to the "No HH" level, one curve for each of the levels for one, two, three, and four previous HH events in increasingly lighter color. Note that this panel has a different HR scale from the other three. DM, diabetes.

Complications Trial (DCCT) trial in patients with type 1 diabetes, the current study observed a positive association of HH with increasing HbA_{1c} >60 mmol/mol (15,18). Lipska et al. (19) reported a U-shaped relationship and increased risk of HH with HbA_{1c} levels lower or higher than the normal 6–6.9% (42–52 mmol/mol) level. However, a possible explanation for the observed association is that patients with a high level of HbA_{1c} may have poor self-care as a predisposing factor and may be less familiar with handling hypoglycemia (the same is probably true for the families). On the other hand, as already mentioned, the introduction of new treatment guidelines in Denmark with glycemic target settings (HbA_{1c} 7.5% [58 mmol/mol]) (10) may have prevented some cases of HH associated with strict glycemic control in type 1 diabetes over the last decade.

Albuminuria appeared to be a strong independent marker of HH in our analysis; patients with macroalbuminuria (ACR >30 mg/mmol) had nearly a doubling of risk of HH compared with patients with normoalbuminuria (<3 mg/mmol). None of any previously mentioned studies have examined albuminuria as a predictor of HH in adult patients with type 1 diabetes. Yun et al. (20) in their 10-year follow-up study reported 2.5 times increased risk of HH in patients with type 2 diabetes. Patients with macroalbuminuria in our study might be under more aggressive treatment than their counterpart of patients with normoalbuminuria; and furthermore, macroalbuminuria is a marker of comorbidities, especially chronic kidney

Table 3—Adjusted HRs with 95% CI for HH in patients with type 1 diabetes in the DADD in Denmark, 2006–2012

Characteristics	HR	95% CI	*P* value
Calendar time/year	0.93	0.91–0.96	<0.0001
Sex			
Male	1		
Female	0.90	0.82–0.98	0.011
BMI (5 kg/m^2)	0.91	0.86–0.96	0.001
Systolic blood pressure (10 mmHg)	1.00	0.98–1.03	0.850
Albuminuria (10 fold)	1.28	1.17–1.40	<0.0001
Smoking			
Never smoker	1	1	
Ex-smoker	1.12	0.98–1.28	0.088
Occasional smoker	1.11	0.89–1.39	0.369
Daily smoker	1.10	0.99–1.21	0.068
Antihypertensive drug use			
No	1		
Yes	1.24	1.12–1.37	<0.0001
Dyslipidemia drug use			
No	1		
Yes	1.06	0.96–1.17	0.253
No. of past HH			
1 event	1		
5 events vs. 1 event	3.19	2.62–3.88	0.000
4 events vs. 1 event	2.63	2.20–3.14	0.000
3 events vs. 1 event	2.00	1.70–2.34	0.000
2 events vs. 1 event	1.59	1.38–1.82	0.000
3 events vs. 2 events	1.26	1.06–1.48	0.007
4 events vs. 3 events	1.32	1.08–1.60	0.006
5 events vs. 4 events	1.21	0.97–1.52	0.095

disease, which is widely considered as a risk marker for HH.

Being underweight increased the risk of HH compared with normal-weight patients in our study, although this finding was not statistically significant. These findings are in line with some previous studies (21,22). This study is unable to explain the mechanism behind this connection, although we assume poor nutritional status may potentially imply poor glycogen depots or eating disorder, which might explain this relation.

The main strength of the study lies in the large data set that covers the whole Danish population aged 16 years and older diagnosed with type 1 diabetes in recent years. The follow-up information on HH is individually linked and as such less susceptible to nominator-denominator bias compared with cross-sectional studies. The diagnosis of type 1 diabetes is clinically verified, which facilitated the inclusion of patients diagnosed during adulthood. Almost one in three patients in the population with type 1 diabetes is diagnosed after age 30 years, and information on this group of patients is particularly scarce in the literature. Other strengths are its prospective design with 7 years of follow-up, using register data with precise information about diabetes type, and unbiased hospital-registered HH event records, which indicates a precise estimation of incidence trends of HH in an adult population with type 1 diabetes. Moreover, the study was able to analyze a number of lifestyle-related factors and a wide variety of clinical risk factors of HH in patients with type 1 diabetes.

The study has some limitations. This study is incapable of revealing the total incidence and trends of severe hypoglycemia in type 1 diabetes in Denmark as a lot of severe hypoglycemia cases are treated at home by family members and acute ambulance services at prehospital triage (7,23–26). Furthermore, we were unable to distinguish whether the events of "hospitalized hypoglycemia" occurred as inpatient or outpatient or emergency care visits. The quality of the Danish National Patient Register data is often discussed and a few studies reported minor misclassification, especially where the coding practice is not clear (27–29). However, these misclassifications are nondifferential (27–29) and unlikely to influence the observed trends. Also, we did not have information on insulin type, ethnicity, socioeconomic status, lifestyle factors (including missing meals, alcohol intake, and exercise), hypoglycemia awareness, or diabetes education, which might influence the incidence of HH (30,31). As hypoglycemia unawareness may be a major risk factor for HH and may furthermore be an important factor underlying the association between diabetes duration and poor control with HH, systematic registration of hypoglycemia awareness in the quality registers would be useful for both clinical and research purposes.

In conclusion, this study of recent trends of HH in adult patients with type 1 diabetes revealed low incidence rates of HH, with a decreasing trend of incidence in Denmark from 2006 to 2012. However, due to increasing incidence of type 1 diabetes combined with a decline in mortality (32), the absolute number of cases of HH will probably continue to increase in the coming decades.

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References

1. Cryer PE. *Hypoglycemia: Pathophysiology, Diagnosis, and Treatment*. New York, Oxford University Press, 1997

2. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. Nat Rev Endocrinol 2014;10:711–722
3. Kaufman FR, Halvorson M, Miller D, Mackenzie M, Fisher LK, Pitukcheewanont P. Insulin pump therapy in type 1 pediatric patients: now and into the year 2000. Diabetes Metab Res Rev 1999;15:338–352
4. Jørgensen ME, Kristensen JK, Reventlov Husted G, Cerqueira C, Rossing P. The Danish Adult Diabetes Registry. Clin Epidemiol 2016;8:429–434
5. Wang J, Geiss LS, Williams DE, Gregg EW. Trends in emergency department visit rates for hypoglycemia and hyperglycemic crisis among adults with diabetes, United States, 2006-2011. PLoS One 2015;10:e0134917
6. Pathak RD, Schroeder EB, Seaquist ER, et al. Severe hypoglycemia requiring medical intervention in a large cohort of adults with diabetes receiving care in U.S. integrated health care delivery systems: 2005-2011. Diabetes Care 2016;39:363–370
7. Leese GP, Wang J, Broomhall J, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care 2003;26:1176–1180
8. Parsaik AKCR, Carter RE, Myers LA, et al. Population-based study of hypoglycemia in patients with type 1 diabetes mellitus requiring emergency medical services. Endocr Pract 2012;18:834–841
9. Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. JAMA Intern Med 2014;174:1116–1124
10. Norgaard K, Olsen B. Changing Denmark from a non-user country to a place using insulin pumps: a story on the initiatives taken. Infusystems Int 2011;10:25–29
11. Swift PG; International Society for Pediatric and Adolescent Diabetes. ISPAD clinical practice consensus guidelines 2006-2007. Diabetes education. Pediatr Diabetes 2007;8:103–109
12. Fredheim S, Johansen A, Thorsen SU, et al.; Danish Society for Diabetes in Childhood and Adolescence. Nationwide reduction in the frequency of severe hypoglycemia by half. Acta Diabetol 2015;52:591–599
13. Pedersen-Bjergaard U, Færch L, Allingbjerg ML, Agesen R, Thorsteinsson B. The influence of new European Union driver's license legislation on reporting of severe hypoglycemia by patients with type 1 diabetes. Diabetes Care 2015;38:29–33
14. Mühlhauser I, Overmann H, Bender R, Bott U, Berger M. Risk factors of severe hypoglycaemia in adult patients with type I diabetes–a prospective population based study. Diabetologia 1998;41:1274–1282
15. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes 1997;46:271–286
16. Donnelly LA, Morris AD, Frier BM, et al.; DARTS/MEMO Collaboration. Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. Diabet Med 2005;22:749–755
17. Bloomfield HE, Greer N, Newman D, et al. *Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes - A Systematic Review of the Evidence*. Washington, DC, U.S. Department of Veterans Affairs, 2012
18. Bott S, Bott U, Berger M, Mühlhauser I. Intensified insulin therapy and the risk of severe hypoglycaemia. Diabetologia 1997;40:926–932
19. Lipska KJ, Warton EM, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. Diabetes Care 2013;36:3535–3542
20. Yun JS, Ko SH, Ko SH, et al. Presence of macroalbuminuria predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. Diabetes Care 2013;36:1283–1289
21. Giorda CB, Ozzello A, Gentile S, et al.; HYPOS-1 Study Group of AMD. Incidence and risk factors for severe and symptomatic hypoglycemia in type 1 diabetes. Results of the HYPOS-1 study. Acta Diabetol 2015;52:845–853
22. Sämann A, Lehmann T, Heller T, et al. A retrospective study on the incidence and risk factors of severe hypoglycemia in primary care. Fam Pract 2013;30:290–293
23. Anderson M, Powell J, Campbell KM, Taylor JR. Optimal management of type 2 diabetes in patients with increased risk of hypoglycemia. Diabetes Metab Syndr Obes 2014;7:85–94
24. Bjork E, Palmer M, Schvarcz E, Berne C. Incidence of severe hypoglycaemia in an unselected population of patients with insulin-treated diabetes mellitus, with special reference to autonomic neuropathy. Diabetes Nutr Metab 1990
25. Frier BM. Hypoglycaemia in the diabetic adult. Baillieres Clin Endocrinol Metab 1993;7:757–777
26. Potter J, Clarke P, Gale EA, Dave SH, Tattersall RB. Insulin-induced hypoglycaemia in an accident and emergency department: the tip of an iceberg? Br Med J (Clin Res Ed) 1982;285:1180–1182
27. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39(Suppl.):30–33
28. Green A. Danish clinical databases: an overview. Scand J Public Health 2011;39(Suppl.):68–71
29. Lidegaard O, Vestergaard CH, Hammerum MS. Quality monitoring based on data from the Danish National Patient Registry. Ugeskr Laeger 2009;171:412–415 [in Danish]
30. Pedersen-Bjergaard U. Severe hypoglycaemia in type 1 diabetes: impact of the renin-angiotensin system and other risk factors. Dan Med Bull 2009;56:193–207
31. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care 1994;17:697–703
32. Jørgensen ME, Almdal TP, Carstensen B. Time trends in mortality rates in type 1 diabetes from 2002 to 2011. Diabetologia 2013;56:2401–2404