# Incidence and Trends in Hypoglycemia Hospitalization in Adults With Type 1 and Type 2 Diabetes in England, 1998–2013: A Retrospective Cohort Study

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## OBJECTIVE

**To determine trends in hospitalization for hypoglycemia in adults with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) in England.**

## RESEARCH DESIGN AND METHODS

**Adults with T1DM or T2DM were identified from 398 of the 684 practices within the Clinical Practice Research Datalink, for which linkage to the Hospital Episode Statistics was possible. Hypoglycemia as the primary reason for hospitalization between 1998 and 2013 was extracted. Trends were estimated using joinpoint regression models for adults with T1DM, young and middle-aged adults with T2DM (18–64 years), and elderly adults with T2DM (≥65 years), respectively.**

## RESULTS

**Among 23,246 adults with T1DM, 1,591 hypoglycemia hospitalizations occurred during 121,262 person-years. Among 241,441 adults with T2DM, 3,738 hypoglycemia hospitalizations occurred during 1,344,818 person-years. In adults with T1DM, the incidence increased 3.74% (95% CI 1.70–5.83) annually from 1998 to 2013. In young and middle-aged adults with T2DM, the annual incidence increase was 4.12% (0.61–7.75) from 1998 to 2013. In elderly adults with T2DM, the incidence increased 8.59% (5.76–11.50) annually from 1998 to 2009, and decreased 8.05% (−14.48 to −1.13) annually from 2009 to 2013, but the incidence was still higher in 2013 than 1998 (adjusted rate ratio 3.01 [1.76–5.14]). Trends in $HbA_{1c}$ level did not parallel trends of hypoglycemia hospitalization for both diabetes types. A possible reason for declined hypoglycemia trend in 2009–2013 in elderly adults with T2DM may be continuously decreased sulfonylurea use after 2009, which was not seen in young and middle-aged adults with T2DM.**

## CONCLUSIONS

**Hypoglycemia requiring hospitalization has been an increasing burden in adults with T1DM and T2DM in England in the previous two decades, with the exception of the decline in elderly adults with T2DM starting in 2009.**


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Hypoglycemia is a common but preventable complication in diabetes (1). In the past few decades, tremendous progress in diabetes management has been made, including the shift in diabetes guidelines from emphasizing hyperglycemia control toward recommending individualized glycemic targets to balance hyper- and hypoglycemia risk (2,3), introduction of new drugs (e.g., dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors) that are associated with low hypoglycemia risk (4,5), and availability of new technologies such as continuous glucose monitoring and insulin pump (6,7). However, it is not clear whether these trends in diabetes management have led to a decline in hypoglycemia risk in adults with diabetes. Particularly, it is not clear if trends of hypoglycemia differ by diabetes type.

The etiology and treatment of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are different, leading to very different hypoglycemia risk (1). Long-term trend studies on hypoglycemia that do not distinguish diabetes type are not able to provide clear data for informing targeted practice-level and policy-level intervention. Previous studies focused on describing hypoglycemia trends in a health care system or in people with diabetes without regard to type (8–13). To our knowledge, for adults with T1DM, only one Danish study reported decreased trends for hospitalization for hypoglycemia from 2006 to 2012 (14). Only two studies reported trends of severe hypoglycemia specifically in adults with T2DM, but with different findings. Lipska et al. (15) found stable rates of severe hypoglycemia between 2006 and 2013 in the U.S. Chen et al. (16) reported a 10-year increase (2000–2010) in the incidence of hypoglycemia-related emergency department visits in Taiwan.

In the current study, we aimed to study hypoglycemia that requires hospital admission, which is a most severe form of hypoglycemia and associated with considerable morbidity, mortality, and health care resource use and expenditure (17). In England, trends of hypoglycemia hospitalization were recently reported by Zaccardi et al. (12) in the entire health care system, but diabetes type–specific trends were unknown. The main goal of our study was to characterize incidence and trends of hypoglycemia hospitalization among adults with T1DM or T2DM between 1998 and 2013, both overall and according to key patient characteristics. Data were from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) from the U.K. We hypothesized that the annual incidence increased first because of emphasizing hyperglycemia control since the Diabetes Control and Complications Trial (DCCT) (18) and then decreased due to *1*) recent recommendations of individualized glycemic management for hypoglycemia risk reduction and *2*) negative findings on the cardiovascular benefits of more aggressive glycemic control therapy from the three randomized trials published in 2008 and 2009, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (19), the Action in Diabetes and Vascular Disease (ADVANCE) trial (20), and the Veterans Affairs Diabetes Trial (VADT) (21). Trends in hypoglycemia hospitalization may vary by diabetes type and patient characteristics.

## RESEARCH DESIGN AND METHODS

### Data Sources

Established in 1987, the CPRD included 684 practices from England, Scotland, Wales, and Northern Ireland and contained over 15 million patient records as of January 2015. Patients in the CPRD are broadly representative of age, sex, and ethnicity of the U.K. population (22). Clinical entries in the CPRD are coded using Read codes, a hierarchical clinical coding system used in general practice in the U.K. (23). The HES is a data warehouse storing records of all patients admitted to National Health Service hospitals in England only. Patient-level data from consenting CPRD practices are linked to the HES data via a trusted third party (22). The HES data used for the current study included admitted patient care information from 1 April 1997 to 31 March 2014. ICD-10 codes are used within the HES. Hypoglycemia hospitalizations were identified from the HES. All other information, including diabetes diagnosis, demographics, and prescriptions, was extracted from the CPRD. The study protocol (15_259RA) was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency in the U.K. and the institutional review boards at the University of North Carolina at Chapel Hill in the U.S.

### Definition of T1DM and T2DM

As of 31 March 2014, 398 of the 684 CPRD practices were linked to the HES and thus were included in our study, accounting for ~60% of the entire CPRD population. The linked CPRD-HES population is representative of the entire CPRD population (24). Patients with one or more diabetes-related Read code were first identified (25). Patients were then excluded if they had any record of secondary diabetes, maturity-onset diabetes of young, latent autoimmune diabetes in adults, or malnutrition-related diabetes or did not meet the research standards established by the CPRD team. Patients were labeled as "unacceptable" by the CPRD team who were identified by a systematic process with noncontinuous follow-up or poor data recording based on a number of prespecified data quality metrics.

Criteria to identify diabetes type were adopted from relevant CPRD literature, with modifications to reflect specific differentiation between T1DM and T2DM (26–28). Among those with at least one diabetes-related code, T1DM was identified if one of the following criteria was met: *1*) one or more T1DM code and use of insulin only; *2*) one or more T1DM code and use of insulin only on the diagnosis date and noninsulin glucose-lowering drug (NIGLD), if any, was introduced 6 months later; or *3*) two or more insulin prescriptions only and one or more unspecified diabetes code. T2DM was defined as any of the following: *1*) two or more T2DM codes and zero T1DM codes, regardless of drug use; *2*) one or more T2DM codes and zero T1DM codes and NIGLD only; *3*) one or more T2DM codes and zero T1DM codes and on NIGLD and insulin, but NIGLD prescribed no later than insulin; *4*) two or more classes of NIGLD; or *5*) two or more prescriptions of a noninsulin, nonmetformin glucose-lowering drug only and one or more unspecified diabetes code. NIGLDs included metformin, sulfonylureas, glinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide 1 receptor agonists, and acarbose.

### Study Period and Definition of Hypoglycemia Hospitalization

The study period was between 1 January 1998 and 31 December 2013 when full-year HES data were available. The follow-up started at the maximum date of the

following: 1 January 1998, first diabetes visit, patient registration, up to standard (UTS) date, or 18 years old. UTS is the date at which the practice data are deemed to be of research quality (22). Follow-up ended at the minimum date of the following: 31 December 2013, death, transfer out, or last data collection for the practice. Hypoglycemia (E16.0, E16.1, and E16.2) listed as the primary diagnosis for hospitalization during the follow-up period was identified. We included all episodes of hypoglycemia hospitalization.

### Statistical Analysis

All analyses were performed separately for T1DM and T2DM. Treatment guidelines for T2DM vary according to an individual's hypoglycemia risk factors, such as age, current use of glucose-lowering drugs, number of comorbidities, duration of diabetes, history of severe hypoglycemia, and life expectancy (2,3). Therefore, separate analyses were performed in young and middle-aged adults with T2DM (18–64 years) and elderly adults with T2DM (≥65 years).

Incidence rates of hypoglycemia hospitalization were calculated by dividing the total number of hypoglycemia hospitalization by total accumulated person-years with diabetes within each year between 1998 and 2013. The accumulated person-years for a patient were obtained by subtracting the follow-up start date from the follow-up end date, which was then divided by 365.25. Stratified incidence rates were also computed. For adults with T1DM, incidence rates were calculated by age (18–44, 45–64, 65–79, and ≥80 years), sex, and length of recorded diabetes history (as an alternative for diabetes duration: 0–4, 5–9, 10–14, and ≥15 years). For young and middle-aged adults with T2DM, incidence rates were calculated by age (18–44 and 45–64 years), sex, length of recorded diabetes history (0–9 and ≥10 years), and current use of glucose-lowering drugs (insulin with/without NIGLD, sulfonylureas with/without other NIGLD, and "other"). For elderly adults with T2DM, incidence rates were calculated by age (65–79 and ≥80 years), sex, length of recorded diabetes history (0–4, 5–9, 10–14, and ≥15 years), and current use of glucose-lowering drugs (insulin only, insulin and NIGLD, sulfonylureas only, sulfonylureas and other NIGLD, and "other"). All rates were reported per 1,000 person-years.

We applied joinpoint regression models to quantify trends for both overall and stratified incidence rates (29). Each joinpoint (i.e., specific year) denoted a statistically significant change in trend. We fitted a heteroscedastic and uncorrelated error joinpoint regression model and allowed a maximum of three joinpoints. A grid search was used to identify locations of joinpoint(s). We selected the best-fitting model by conducting a series of permutation tests based on 4,500 Monte Carlo replicates, using a Bonferroni correction for multiple testing (30). Parameters in the model were estimated using weighted least squares, with weights proportional to the inverse of the variance of the incidence rate at each year. Annual percentage change and 95% CI were estimated.

Two sensitivity analyses were conducted to evaluate whether the potential misclassification of diabetes type may impact obtained hypoglycemia trends. First, the proportion of patients identified by each criterion of our case definition was calculated. We reran joinpoint regression models to determine trends after removing patients identified by the criteria that from a clinical perspective were most likely associated with misclassification. Second, we considered definitions for T1DM and T2DM used in three previous CPRD studies (26–28). For T1DM, the T1DM case definitions in the CPRD literature generally included young age, such as <35 years, as a criterion. However, it is well known that the T2DM prevalence has been increasing in children and young adults (31). Thus, hypoglycemia trends were not examined using exactly the same published definitions for T1DM because of the potential to incorrectly include individuals with T2DM. For T2DM, we reran joinpoint analyses using the same definitions as previously used in the CPRD (26–28).

To compare the difference of the incidence of hypoglycemia hospitalization by year, we fitted a negative binomial regression model with the number of hospitalizations as the outcome and the logarithm of person-years as the offset. Using year 1998 as the reference, we included 15 dummy year variables, representing subsequent years from 1999 to 2013 and adjusted for age, sex, length of recorded diabetes history, and current use of glucose-lowering drugs. Incidence rate ratio (IRR) and 95% CI were estimated. We also described the changes over time in glycemic control (i.e., $HbA_{1c}$), glucose-lowering drugs, age, length of recorded diabetes history, BMI, and Charlson comorbidity score (32) to help understand the changes of the study population's characteristics. SAS (version 9.4; SAS Institute Inc.) and Joinpoint software were used to perform analyses (29). Statistical significance was indicated by a two-sided $P$ value $<0.05$.

## RESULTS

Among 23,246 adults with T1DM (Fig. 1), 1,591 hypoglycemia hospitalizations occurred during 121,262 follow-up years (Supplementary Table 1). Among 241,441 adults with T2DM, 553 hypoglycemia hospitalizations were documented during 560,686 person-years of follow-up among young and middle-aged adults, and 3,185 hospitalizations were documented during 784,132 person-years of follow-up among elderly adults.

In adults with T1DM (Supplementary Table 1), the incidence increased from 9.57 to 14.80 hospitalizations for hypoglycemia per 1,000 person-years between 1998 and 2013 (adjusted IRR 1.67 [95% CI 1.14–2.43]). The incidence of hypoglycemia hospitalization increased 3.74% ([1.70–5.83], $P$ = 0.001) annually (Table 1 and Fig. 2*A*). This increasing trend was seen in all age subgroups (Supplementary Fig. 1*A*) and in males and females (Supplementary Fig. 1*B*). However, the significant increasing trend was found only in those with the longest length of recorded diabetes history (Supplementary Fig. 1*C*).

In young and middle-aged adults with T2DM, the incidence increased from 0.73 to 1.19 hospitalizations for hypoglycemia per 1,000 person-years between 1998 and 2013 (adjusted IRR 1.52 [0.68–3.38]). The annual percent increase was 4.12% (0.61–7.75, $P$ = 0.02) (Table 1 and Fig. 2*B*). This increasing trend was similar between young (18–44 years) and middle-aged adults (45–64 years) (Supplementary Fig. 2*A*), between males and females (Supplementary Fig. 2*C*), and between short and long length of recorded diabetes history ≥10 years (Supplementary Fig. 2*E*), respectively. The incidence increased among current insulin users but not current sulfonylureas users and "other" users (Supplementary Fig. 2*G*).

In elderly adults with T2DM, the incidence was 1.12 and 3.52 hospitalizations for hypoglycemia per 1,000 person-years

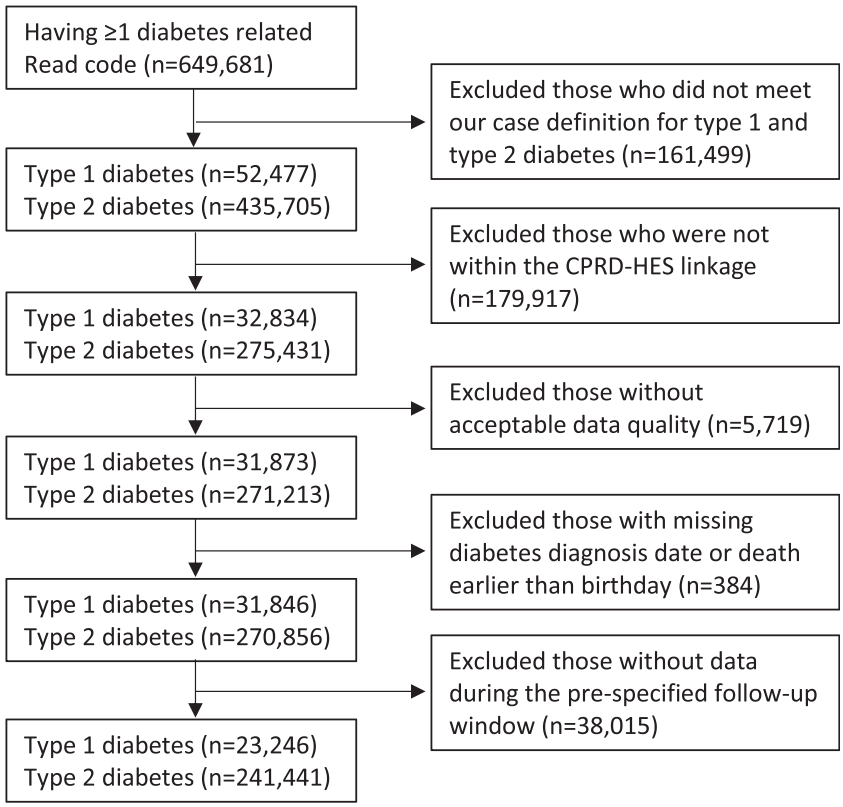


**Figure 1**—Flowchart of identification of T1DM and T2DM.

in 1998 and 2013, respectively (adjusted IRR 3.01 [1.76–5.14]). The incidence increased 8.59% (5.76–11.50, $P < 0.0001$) annually from 1998 to 2009 and decreased 8.05% (−14.48 to −1.13, $P = 0.03$) annually from 2009 to 2013 (Table 1 and Fig. 2*C*). This nonlinear trend was observed among two subgroups of age (65–79 and ≥80 years) (Supplementary Fig. 2*B*) and both sex groups (Supplementary Fig. 2*D*). The trend differed by length of recorded diabetes history (Supplementary Fig. 2*F*). The incidence rate did not change among those with the shortest length of recorded diabetes history (0–4 years). A nonlinear trend was seen in the remaining three groups with longer length of recorded diabetes history. The temporal trend differed by current use of glucose-lowering drug(s) (Supplementary Fig. 2*H*). There was a linear increasing trend in all groups, except users of both insulin and NIGLD, among whom a decline was observed since 2009. Removing current insulin and NIGLD users or two groups with long length of recorded diabetes history (10–14 and ≥15 years) from the analyses did not alter the change in the trend happening in 2009 (Supplementary Table 2).

The mean $HbA_{1c}$ level did not change much among adults with T1DM from 1998 to 2013 (Fig. 3*A*). The proportion of individuals with $HbA_{1c}$ <6.5% (47.5 mmol/mol) decreased and the other four higher $HbA_{1c}$ groups generally remained stable. The mean $HbA_{1c}$ level decreased among adults with T2DM (Fig. 3*B* and *C*) before 2009 and then started to rise. In young and middle-aged adults with T2DM, the proportion of individuals with $HbA_{1c}$ ≥8.5% (69.4 mmol/mol) decreased whereas the proportion of individuals with $HbA_{1c}$ 6.5–7.4% (47.5–57.4 mmol/mol) increased; the remaining two $HbA_{1c}$ groups remained relatively unchanged. In elderly adults with T2DM, a decreased proportion in the three higher $HbA_{1c}$ groups was seen whereas an increased proportion was observed in the two lower $HbA_{1c}$ groups.

For T2DM, the trends in the current use of all classes of glucose-lowering drugs were similar between young and middle-aged adults (Supplementary Fig. 3*A*) and elderly adults (Supplementary Fig. 3*B*), except that the current use of sulfonylureas decreased during the entire period in elderly adults, whereas in young and middle-aged adults, the decrease was only seen before 2007. The average age declined in adults with T1DM and slightly declined in young and middle-aged adults with T2DM but slightly increased in elderly adults with T2DM (Supplementary Fig. 4*A*). For adults with T1DM and T2DM, we observed increased length of recorded diabetes history (Supplementary Fig. 4*B*), elevated BMI (Supplementary Fig. 4*C*), and higher Charlson comorbidity score over time (Supplementary Fig. 4*D*).

The sensitivity analyses indicated the robustness of our results. The criteria that were most likely to misclassify diabetes type only captured a small proportion of patients with T1DM (11.86%) and T2DM (0.33%) (Supplementary Tables 3 and 4). Removing them from analyses did not change the results (Supplementary Table 5). Of note, 14.72% of patients with T1DM who were exclusively taking insulin and had one or more T1DM code also had a T2DM code (Supplementary Table 3). Further excluding these patients did not change trends of hypoglycemia hospitalization in T1DM (annual percent increase 2.48% [0.10–4.91], $P = 0.04$). In addition, the hypoglycemia trends estimated using exactly the same published T2DM case definitions were similar to the trends obtained using our definition (Supplementary Table 6).

## CONCLUSIONS

In England, the incidence of hypoglycemia hospitalization increased from 1998 to 2013 among both adults with T1DM and young and middle-aged adults with T2DM. In elderly adults with T2DM, after a sharp increase in years prior to 2009, a decline in the incidence of hypoglycemia hospitalization was observed between 2009 and 2013. Nonetheless, the incidence in 2013 was still three times that in 1998. Subgroup analyses did not find a difference in hypoglycemia hospitalization trends by age and sex, but heterogeneity was found by glucose-lowering drugs. The $HbA_{1c}$ trends alone could not explain hypoglycemia hospitalization trends. Continuously decreased use of sulfonylureas may be a possible reason for the declined hypoglycemia hospitalization trend since 2009 among elderly adults with T2DM.

A complicating factor for interpreting $HbA_{1c}$ data is the introduction of the Quality and Outcomes Framework (QOF)

**Table 1—Trends in hypoglycemia hospitalization by diabetes type**

| | Trend 1 | | | Trend 2 | | | Trend 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Period | APC (95% CI) | *P* | Period | APC (95% CI) | *P* | Period | APC (95% CI) | *P* |
| Adults with T1DM | | | | | | | | | |
| Overall | 1998–2013 | 3.74 (1.70 to 5.83) | 0.001 | | | | | | |
| Age-group | | | | | | | | | |
| 18–44 years | 1998–2013 | 3.91 (0.42 to 7.52) | 0.03 | | | | | | |
| 45–64 years | 1998–2013 | 5.12 (1.65 to 8.70) | 0.01 | | | | | | |
| 65–79 years | 1998–2013 | 3.48 (0.59 to 6.46) | 0.02 | | | | | | |
| ≥80 years | 1998–2013 | 6.71 (3.52 to 9.99) | 0.0004 | | | | | | |
| Sex | | | | | | | | | |
| Male | 1998–2013 | 3.36 (1.41 to 5.34) | 0.002 | | | | | | |
| Female | 1998–2013 | 4.13 (1.43 to 6.89) | 0.005 | | | | | | |
| Diabetes duration | | | | | | | | | |
| 0–4 years | 1998–2013 | 2.67 (−0.77 to 6.22) | 0.12 | | | | | | |
| 5–9 years | 1998–2013 | 0.47 (−3.38 to 4.47) | 0.80 | | | | | | |
| 10–14 years | 1998–2013 | −0.14 (−2.97 to 2.76) | 0.92 | | | | | | |
| ≥15 years | 1998–2013 | 4.97 (2.66 to 7.33) | 0.0004 | | | | | | |
| Young and middle-aged adults with T2DM | | | | | | | | | |
| Overall | 1998–2013 | 4.12 (0.61 to 7.75) | 0.02 | | | | | | |
| Age-group | | | | | | | | | |
| 18–44 years | 1998–2013 | 4.23 (−0.99 to 9.73) | 0.11 | | | | | | |
| 45–64 years | 1998–2013 | 3.90 (0.18 to 7.76) | 0.04 | | | | | | |
| Sex | | | | | | | | | |
| Male | 1998–2013 | 4.04 (0.04 to 8.21) | 0.048 | | | | | | |
| Female | 1998–2013 | 3.77 (−1.01 to 8.77) | 0.11 | | | | | | |
| Diabetes duration | | | | | | | | | |
| <10 years | 1998–2013 | 3.53 (−0.98 to 8.25) | 0.12 | | | | | | |
| ≥10 years | 1998–2013 | 1.82 (−2.22 to 6.04) | 0.36 | | | | | | |
| Current status of glucose-lowering drug use | | | | | | | | | |
| Insulin with/without NIGLD | 1998–2013 | 5.76 (1.11 to 10.64) | 0.02 | | | | | | |
| Sulfonylureas with/without NIGLD | 1998–2013 | 1.42 (−2.87 to 5.90) | 0.50 | | | | | | |
| Other* | 1998–2013 | 2.93 (−2.08 to 8.20) | 0.23 | | | | | | |
| Elderly adults with T2DM | | | | | | | | | |
| Overall | 1998–2009 | 8.59 (5.76 to 11.50) | <0.0001 | 2009–2013 | −8.05 (−14.48 to −1.13) | 0.03 | | | |
| Age-group | | | | | | | | | |
| 65–79 years | 1998–2009 | 8.28 (4.96 to 11.71) | 0.0002 | 2009–2013 | −8.13 (−16.11 to 0.61) | 0.06 | | | |
| ≥80 years | 1998–2008 | 8.86 (4.02 to 13.93) | 0.002 | 2008–2013 | −6.41 (−12.45 to 0.06) | 0.052 | | | |
| Sex | | | | | | | | | |
| Male | 1998–2009 | 9.00 (5.33 to 12.79) | 0.0002 | 2009–2013 | −6.13 (−14.30 to 2.83) | 0.15 | | | |
| Female | 1998–2009 | 8.18 (4.41 to 12.08) | 0.0005 | 2009–2013 | −9.92 (−18.50 to −0.43) | 0.04 | | | |
| Diabetes duration | | | | | | | | | |
| 0–4 years | 1998–2013 | −1.38 (−4.87 to 2.23) | 0.42 | | | | | | |
| 5–9 years | 1998–2002 | 24.29 (−5.62 to 63.67) | 0.11 | 2002–2013 | −6.51 (−9.54 to −3.38) | 0.0009 | | | |

*Continued on p. 1656*

**Table 1—Continued**

| | Trend 1 | | | Trend 2 | | | Trend 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Period | APC (95% CI) | *P* | Period | APC (95% CI) | *P* | Period | APC (95% CI) | *P* |
| 10–14 years | 1998–2005 | 3.12 (−3.19 to 9.85) | 0.29 | 2005–2008 | 17.90 (−9.17 to 53.03) | 0.18 | 2008–2013 | −12.95 (−17.16 to −8.52) | 0.0002 |
| ≥15 years | 1998–2008 | 16.60 (8.21 to 25.64) | 0.0009 | 2008–2013 | −6.32 (−13.67 to 1.66) | 0.11 | | | |
| Current status of glucose-lowering drug use | | | | | | | | | |
| Sulfonylureas only | 1998–2013 | 9.42 (5.11 to 13.91) | 0.0003 | | | | | | |
| Sulfonylureas + other NIGLD | 1998–2013 | 3.74 (0.86 to 6.71) | 0.01 | | | | | | |
| Insulin only | 1998–2013 | 7.62 (4.34 to 11.01) | 0.0002 | | | | | | |
| Insulin + NIGLD | 1998–2009 | 9.50 (3.98 to 15.30) | 0.003 | 2009–2013 | −8.71 (−19.92 to 4.06) | 0.15 | | | |
| Other* | 1998–2013 | −0.39 (−5.29 to 4.77) | 0.87 | | | | | | |

APC, annual percent change. *Included self-management alone (i.e., not currently taking any glucose-lowering drug), NIGLD monotherapy (excluding sulfonylureas), or combinations of any glucose-lowering drugs (excluding insulin and sulfonylureas).

in 2004, under which general practitioners have been financially incentivized to meet clinical targets for patients with diabetes. Kontopantelis et al. (33) found that the QOF introduction did not impact the already decreasing trend of the $HbA_{1c}$ level during the study period 2000–2007. Inappropriate glycemic control is a known risk factor for hypoglycemia (34,35). However, our data showed that the $HbA_{1c}$ trends did not parallel the trends in hypoglycemia hospitalization. As reported by the DCCT study (34), change in $HbA_{1c}$ level itself could only explain a small proportion of the variation (<10%) for hypoglycemia risk. Also, the $HbA_{1c}$ level is determined by a wide range of factors (e.g., demographics, duration of diabetes, glucose-lowering therapy and adherence, diet, physical activity, and overall health condition), and most of these factors may also influence hypoglycemia risk dependent or independent of $HbA_{1c}$ (36). The comparison of $HbA_{1c}$ trends with hypoglycemia trends at a population level is further complicated by the U-shaped association between $HbA_{1c}$ level and hypoglycemia risk found in T2DM (35).

According to our analyses, an increase was seen in length of recorded diabetes history, BMI, and Charlson comorbidity score. However, this increase may be the consequence of both population aging and more complete data recording within the CPRD over time, particularly after the QOF introduction (22,33). Thus, we are not certain about the true effect of population aging on observed trends in hypoglycemia hospitalization in our study. The mean age declined in adults with T1DM and slightly decreased in young and middle-aged adults with T2DM. This may be driven by the rise of childhood T1DM (37,38) and T2DM in children and young adults (31).

The hypoglycemia trend identified in adults with T1DM from our study is opposite that reported from the Danish Register Linkage Cohort study (14), in which a decreasing trend in the incidence of hypoglycemia hospitalization was seen. In fact, although our trends were linear statistically, the incidence of hypoglycemia hospitalization did not change much since 2006 except for the jump in 2010. The Danish study included hypoglycemia hospitalization from outpatient, inpatient, and emergency room visits, whereas our study only analyzed inpatient data. We do not know if hypoglycemia trends differ by data source in the Danish study.

In adults with T2DM, notable differences in trends were found between young and middle-aged adults (i.e., linear increasing trend) and elderly adults (i.e., nonlinear trend), suggesting that age played a crucial role in diabetes management. In addition to the possibly increased vulnerability to hypoglycemia over time because of aging, the increasing trend of hypoglycemia hospitalizations in young and middle-aged adults may be driven by the convincing microvascular benefits of tight glycemic control (18) and diabetes guidelines that individuals with short diabetes duration, few comorbidities, and long life expectancy can be treated with more stringent glycemic control (2,39). Further, the primary cause of death in people with diabetes is cardiovascular disease (40,41). Achieving near-normal glycemic control, even with intensive therapy, may still be the common practice and the priority. Although speculative, the decline in the incidence of hypoglycemia hospitalization starting in 2009 in elderly adults with T2DM may be driven by physicians who may have recently started to treat a proportion of elderly patients with T2DM with less stringent glycemic control who are vulnerable to hypoglycemia. We found that the use of sulfonylureas decreased all the time among elderly adults with T2DM, but the decline stopped around 2007 in young and middle-aged adults with T2DM. Further, well-publicized results in 2008–2009 from three trials (ACCORD [19], ADVANCE [20], and VADT [21]) suggested that elderly adults may not gain macrovascular benefits from aggressive glycemic control; rather, intensive therapy was associated with increased risk of severe hypoglycemia and may increase mortality. With a few exceptions (42,43), most diabetes guidelines did not emphasize, until very recently, adjustment of glycemic targets through evaluating an individual's hypoglycemia risk factors (2,3,44).

Lipska et al. (10) had the same hypothesis that the decreasing trend may be driven by the persuasive findings from the three trials (19–21). The study of Lipska et al. was conducted among U.S. Medicare beneficiaries ≥65 years old. The hospital admission rate for hypoglycemia decreased slightly since 2007 among the entire sample. The decline occurred earlier in 2004 when only Medicare beneficiaries

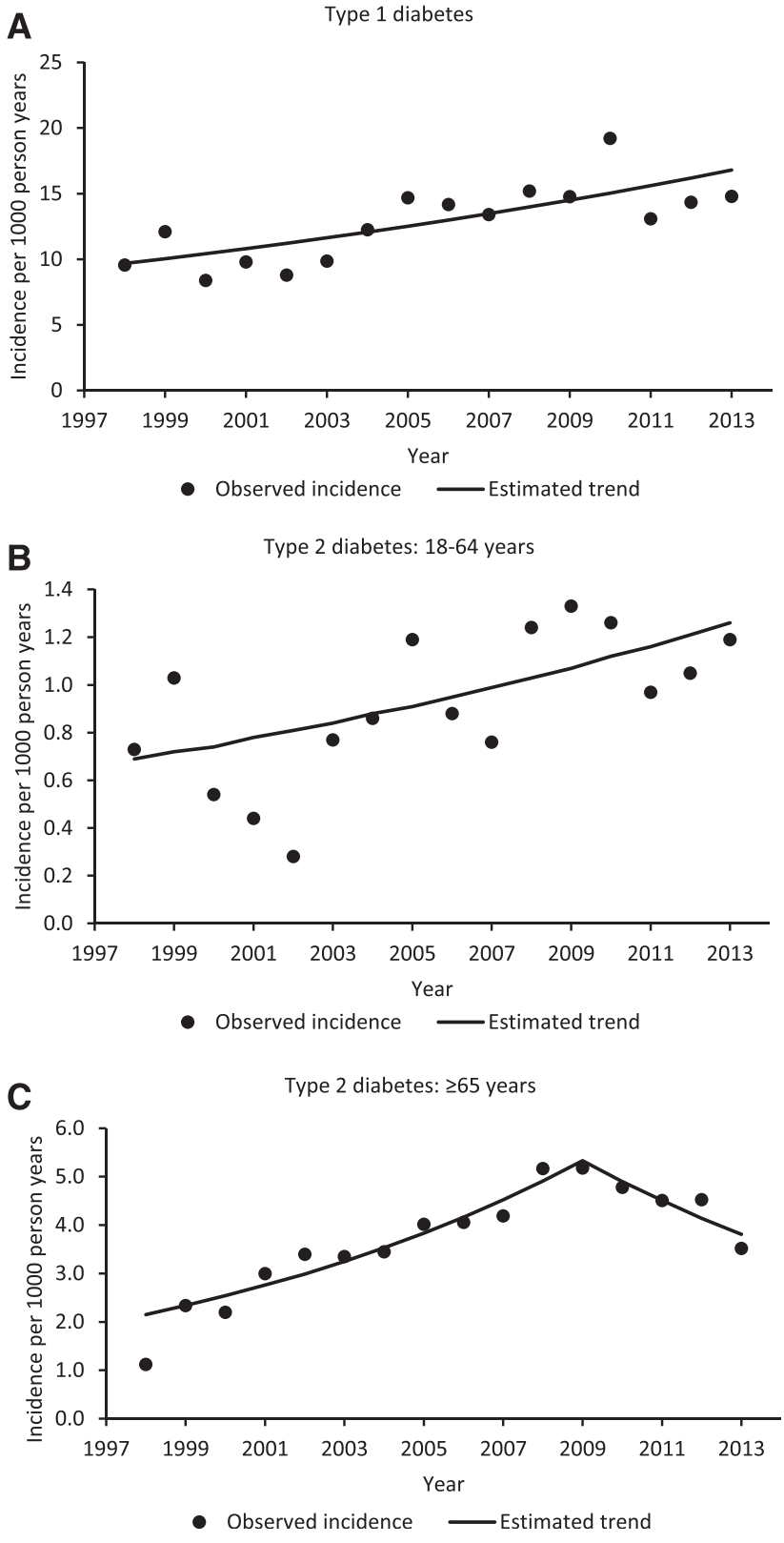


**Figure 2**—Incidence and trends in hypoglycemia hospitalization in adults with T1DM (*A*), young and middle-aged adults with T2DM (*B*), and elderly adults with T2DM (*C*).

with diabetes were analyzed, but diabetes type–specific trend was not reported. Zaccardi et al. (12) reported an increased incidence of hospital admissions for hypoglycemia from 2005 to 2010 and a relatively stable incidence from 2010 to 2014 in England using the HES data. Zaccardi et al. (12) did not examine the trends by diabetes type, although accounting for overall diabetes prevalence led to a reduction of the hypoglycemia hospitalization rate from 2010. Our analyses suggest that the decrease in trends of hypoglycemia hospitalization was only observed in elderly adults with T2DM, not in adults with T1DM or young and middle-aged adults with T2DM.

Subgroup analyses in adults with T2DM revealed important differences in trends by current use of glucose-lowering drugs. In young and middle-aged adults with T2DM, the incidence of hypoglycemia hospitalization was considerably higher among current insulin users than patients who were currently taking NIGLD only. Furthermore, the annual increase rate was also the greatest among current insulin users. Similarly, in elderly adults with T2DM, subgroups (e.g., current insulin or sulfonylurea users) with markedly high incidence of hypoglycemia hospitalization also had a large annual increase in trends, contributing to hypoglycemia burden substantially. Although the incidence of hypoglycemia hospitalization dropped down in current insulin and NIGLD users since 2009, the incidence in 2013 was still much higher than that observed in 1998. In addition, removing them from analyses did not change the overall nonlinear trend, suggesting that the declining trend was not determined by the subgroup who was currently taking insulin and NIGLD.

Hypoglycemia requiring hospital admission only represents <10% of total severe hypoglycemia, defined as an event requiring assistance of another person (45), and ~25% of emergency department visits for hypoglycemia (8). However, treating hypoglycemic episodes resulting in hospital admission is expensive and associated with a significant use of health care resources (17). Approaches known to effectively reduce the risk of hypoglycemia include patient education, dietary and exercise modifications, medication adjustment, careful glucose monitoring by the patient, and conscientious surveillance by the clinician (1). However, choosing appropriate strategies for patients with diabetes should consider each individual's diabetes type, hypoglycemia risk factors, and long-term health goals (1–3,46).

Our study provided informative long-term trend data on the incidence of hypoglycemia hospitalization for both adults with T1DM and adults with T2DM. However,

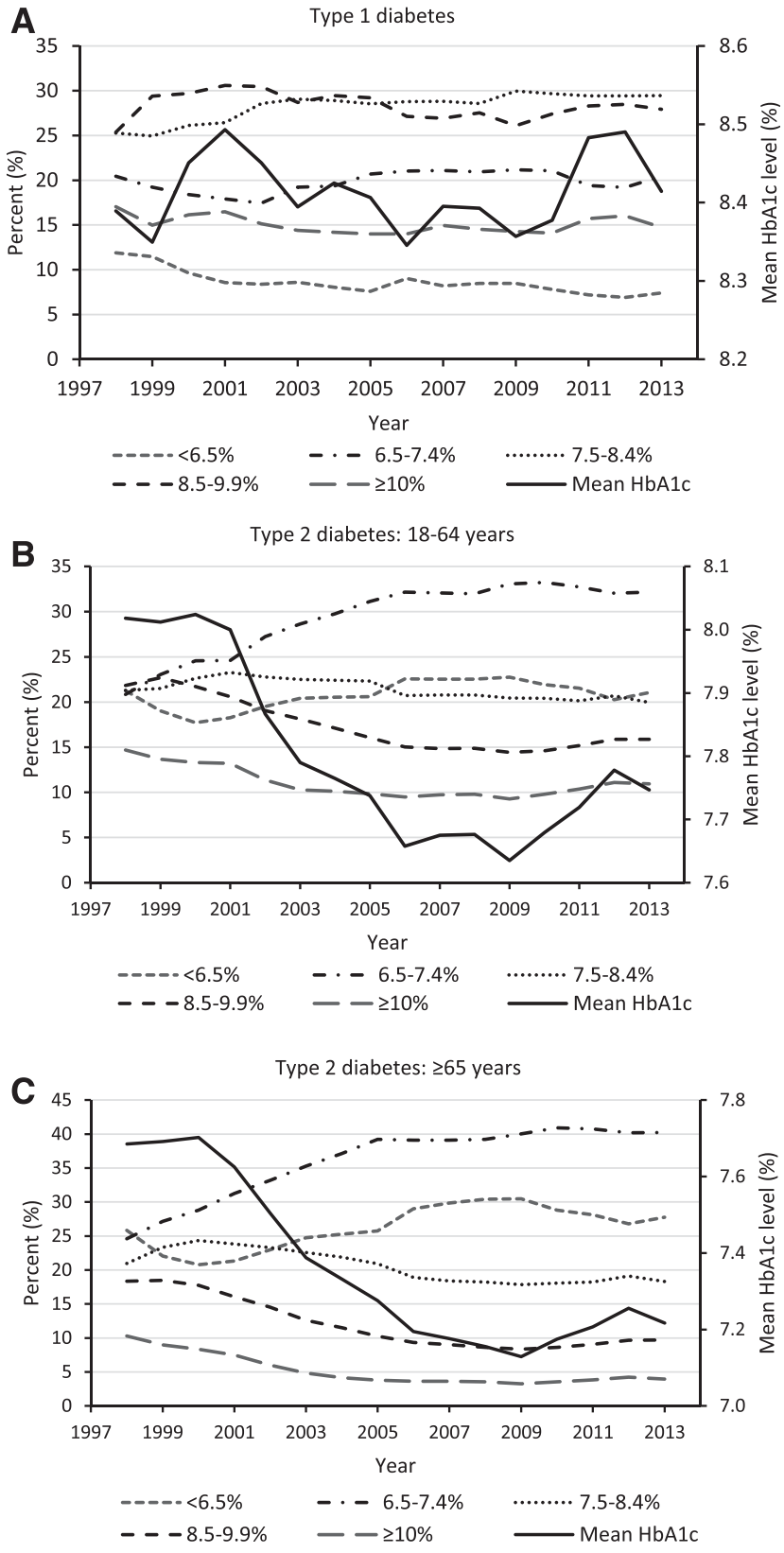


**Figure 3**—Trends in $HbA_{1c}$ level in adults with T1DM (*A*), young and middle-aged adults with T2DM (*B*), and elderly adults with T2DM (*C*).

limitations should be noted. First, misclassification of diabetes type is a common problem by using electronic health data. However, our results were robust and unlikely to be influenced by misclassification error according to the sensitivity analysis findings. Second, we only studied hypoglycemia requiring hospital admission. Our data may not be applied to severe hypoglycemia not leading to hospitalization. Third, the QOF was launched in 2004, and diabetes type–specific Read codes were used since 2006 rather than the high-level general Read code for diabetes. They have resulted in more complete data recorded in the CPRD and facilitated the distinction of diabetes type. A study reported slightly increased T2DM prevalence and decreased diagnosis age after the QOF period (47); adjusting these changes might even demonstrate a larger change in trends, but that is outside the scope of this work. Fourth, the trends in $HbA_{1c}$ and other patient characteristics, such as BMI, may be affected by the missing data, particularly in early years (Supplementary Fig. 5*A* and *B*). The completeness of $HbA_{1c}$ and BMI data already noticeably increased prior to the QOF introduction. Fifth, the first recorded diabetes visit date in the CPRD was used as an approximation for diabetes diagnosis date, which underestimated the duration of diabetes. Sixth, it is not clear if hospital admission criteria for hypoglycemia or the sensitivity to detect hypoglycemia (e.g., more use of glucose monitoring devices) might have changed over time; both may impact hospital admission for hypoglycemia. Finally, drug switching between different glucose-lowering drugs over time may be another factor to explain the observed hypoglycemia trends in England. However, our study is not powered to study both current drug users and drug switchers. Current use of glucose-lowering drugs may be most relevant to hypoglycemia as an acute complication.

In conclusion, hypoglycemia that requires hospitalization has been a rapidly growing burden to the health care system in England. The incidence of hypoglycemia hospitalization increased from 1998 to 2013 in adults with T1DM, and in young and middle-aged adults with T2DM. The incidence of hypoglycemia hospitalization remained high in spite of the recent decline in elderly adults with T2DM. Practical approaches for hypoglycemia management to reverse the increasing trend of hypoglycemia hospitalization in England are critically needed. Studies that are able to investigate diabetes type–specific longitudinal trends of severe hypoglycemia not resulting in hospital admission are encouraged. Also,

future work is needed to better understand the contributors of the hypoglycemia trends in England, including the decline from 2009 in elderly patients with T2DM.

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**Author Contributions.** V.W.Z. participated in the study design, acquired and analyzed the data, wrote and revised the manuscript, and contributed to the discussion. J.J. acquired the data, reviewed and edited the manuscript, and contributed to the discussion. S.R.C., E.K., C.M.S., and P.G.-L. reviewed and edited the manuscript and contributed to the discussion. E.J.M.D. participated in the study design, reviewed and edited the manuscript, and contributed to the discussion. V.W.Z. and E.J.M.-D. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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