Risk factors and outcome differences in hypoglycaemia-related hospital admissions

A case–control study in England

Short title: Risk factors and outcomes of admissions for hypoglycaemia

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ABSTRACT

Aims: To evaluate risk factors for hospital admissions for hypoglycaemia and compare length of hospitalisation, inpatient mortality, and hospital readmission between hypoglycaemia and non-hypoglycaemia-related admissions.

Materials and Methods: We used all admissions for hypoglycaemia in people with diabetes to English NHS hospital trusts between 2005 and 2014 (101,475 case admissions) and three random admissions per case in people with diabetes without hypoglycaemia (304,425 control admissions). Risk factors and differences in the three outcomes were estimated with logistic and negative binomial regressions.

Results: A U-shaped relationship between age and risk of admission for hypoglycaemia was observed until the age of 85 years: compared to the nadir at 60 years, the risk was progressively higher in younger and older patients and steadily declined after 85 years. Social deprivation (positively) and comorbidities (negatively) were associated with the risk of admission for hypoglycaemia. Compared to Caucasians, other ethnic groups had lower (Bangladeshi, Pakistani, Indians) or higher (Caribbean) risk of admission for hypoglycaemia. Length of hospitalisation was 26% shorter while risk of rehospitalisation was 65% higher in people admitted for hypoglycaemia. Compared to admissions for hypoglycaemia, risk of inpatient mortality was 50% lower for unstable angina but higher for acute myocardial infarction (3 times), acute renal failure (5), or pneumonia (8).

Conclusions: Among hospital-admitted individuals with diabetes, age, social deprivation, comorbidities, and ethnicity are associated with higher frequency for hospitalisation due to hypoglycaemia. Admission for hypoglycaemia is associated with a greater risk of readmission, a shorter length of hospitalisation, and a generally lower inpatient mortality compared to admissions for other medical conditions. These results could help identifying at-risk groups to reduce the burden of hospitalisation for hypoglycaemia.

INTRODUCTION

In patients living with diabetes, hypoglycaemia is one of most common and feared side effects and is a major barrier to achieving glucose control [1]. Although most hypoglycaemic events are self-treated, less commonly severe episodes necessitate third party support and are potentially associated with a risk of short- and long-term complications including confusion, convulsions, injuries, permanent impairment of cognitive function, and vascular and all-cause death [2-4]. A proportion of severe episodes result in hospital admission and represent a significant burden for patients and healthcare resource utilisation [1, 5, 6].

A recent study reported a rising number of admissions for hypoglycaemia in England from 2005 to 2010, followed by a flat trend until 2014 [7]. Published studies have identified clinical, demographic, and socioeconomic factors associated with the risk of hypoglycaemia [8, 9], although evidence available from large observational studies on the association of these factors with hospitalisation for hypoglycaemia in patients with diabetes is more limited; the identification and estimation of their impact could help recognise at-risk patients and guide the implementation of appropriate individual- and population-level strategies. Moreover, evidence is also limited on differences in outcomes, such as length of hospital stay, inpatient death, and hospital readmission, comparing admissions for hypoglycaemia *vs* those for other causes in people with diabetes [5, 10, 11].

Within this context, we aimed to investigate risk factors for hospital admissions for hypoglycaemia and subsequent outcomes in patients with diabetes in England using a case-control study which included all hospital admissions for hypoglycaemia and a random sample of admissions in subjects with diabetes without hypoglycaemia.

MATERIALS AND METHODS

Study design, setting, and source of data

In this nationwide, retrospective case–control study, data were extracted from the Hospital Episode Statistics database (HES) [12]. HES contains information on all finished consultant episodes in English National Health Service hospital trusts. From 1/1/2005 to 31/12/2014, cases were defined as all hospital admissions reporting the first ICD–10 (International Classification of Diseases, 10th revision) diagnosis field E160 (drug–induced hypoglycaemia without coma), E161 (other hypoglycaemia), or E162 (hypoglycaemia, unspecified) and E10+ (Insulin–dependent diabetes mellitus) or E11+ (Non–insulin–dependent diabetes mellitus) in any of the remaining ICD–10 fields (from 2nd to 20th). Within HES, three control admissions, defined as admissions in subjects with diabetes and without the aforementioned hypoglycaemia ICD–10 codes (E160, E161, or E162) in the first position, were randomly selected for each case; there was no overlap of participants in case and control admissions. For each admission episode, data were available on age, sex, self–reported ethnicity, region of usual residence, start and end date of the episode, admission and discharge method (which reported whether admission resulted in death), and Index of Multiple Deprivation (IMD, a weighted measure of social deprivation including income, employment, health deprivation and disability, education, barriers to housing and services, crime, and living environment); ICD–10 codes were also used to calculate the Charlson comorbidity score [13].

Data analysis

Stata, version 14.1 (Stata Corp, College Station, Texas), was used for all analyses, and results are reported with 95% confidence intervals (CIs); a p–value <0.05 was considered statistically significant.

Characteristics of case and control admissions were reported as mean and standard deviation, median and interquartile range, or number and percentage, as appropriate. We estimated odds ratios (ORs) of

hypoglycaemia-related admission for the risk factor age, sex, ethnicity (African, Bangladeshi, Caribbean, Indian, Pakistani, White, other, and not available), IMD-10 (deciles of IMD), and Charlson score, by fitting logistic regression with calendar year as a factor variable (reference year, 2005) and modelling age with restricted cubic spline (five knots at 5, 27.5, 50, 72.5, and 95 percentiles). We opted for this model given the non-linear relationship between age and risk of admission for hypoglycaemia [7]; all other analyses included untransformed age. We also fitted logistic regression models, adjusted for the same risk factors and calendar year, to estimate the odds of death in people admitted for hypoglycaemia compared to the twenty most common reasons of admission in controls; and to calculate the odds of hospital readmission for hypoglycaemia in people admitted for hypoglycaemia *vs* readmission for any other cause in people not admitted for hypoglycaemia. Lastly, we performed adjusted negative binomial regressions to estimate the ratio of hospital stay in case admissions *vs* control admissions. All regressions used complete records; following a two-stage approach, region-specific coefficients were pooled across regions by random-effects meta-analyses with heterogeneity in the associations estimated by the I^2 statistic.

We performed two sensitivity analyses. First, we used restricted cubic spline with seven (at 2.5, 18.3, 34.2, 50, 65.8, 81.7, 97.5 percentiles) knots. Second, we included admissions where the ICD-10 codes for hypoglycaemia were between position 2 and 5 as cases.

Supplementary analysis

In HES, diabetes phenotypes are codified as “insulin-dependent” (E10+) or “non-insulin-dependent” (E11+). Although in principle they should correspond respectively to type 1 and type 2 diabetes, a definite diagnosis of diabetes type is sometimes difficult and, particularly for administrative data, inaccuracies are possible. Given the expected difference in the relationship between risk of admission for hypoglycaemia and age by diabetes type, we performed a

supplementary stratified analysis and reported details of sample definition and results in the Supplementary Appendix.

RESULTS

Risk factors for admission for hypoglycaemia

Over the 10-year study period, a total of 101,475 hospital admissions for hypoglycaemia were recorded in 79,172 patients with diabetes, of which 82.4% had a single episode (Supplementary Appendix, Table S1 and Table S2). Mean Charlson scores resulted 2.01 and 2.24 for case and controls admissions, respectively, and admissions for hypoglycaemia occurred more in older than younger subjects, although there were more admissions in subjects younger than 20 years old (7.0%) compared to the age group 20–29 (3.4%), 30–39 (3.9%), and 40–49 years (6.0%). A similar pattern of age distribution was found for the 304,425 control admissions, yet the increase for subjects younger than 20 years was less pronounced. In control admissions, around 10% reported “chest pain, unspecified”, “urinary tract infection, site not specified”, or “unspecified acute lower respiratory infection” as first code (Table S3), while ICD–10 codes for hypoglycaemia were reported in the second position in 1,381 out of 300,166 (0.46%) available codes and in third position in 868 out of 287,428 (0.30%) (Table S4).

The relationship between age and risk of admission for hypoglycaemia, adjusted for sex, ethnicity, IMD–10, Charlson score, and calendar year, was U-shaped until the age of around 85 years old with nadir at 60 years (Figure 1). Compared to the nadir, the risk was progressively higher in younger (OR 1.12, 1.51, 2.26, 3.49, and 5.40 at 50, 40, 30, 20, and 10 years old, respectively) and older subjects, with an OR of 1.83 at the age of 85 and a subsequent steadily decline. Such a pattern was regionally consistent (Supplementary Figure S1).

There was no significant association between sex and risk of admission for hypoglycaemia (OR 1.01; 95% CI: 0.97 to 1.05, comparing females vs males) (Figure 2); conversely, all other risk factors were significantly related to risk of admission for hypoglycaemia. With the exception of African ethnicity, other ethnic groups had lower or higher risk compared to Caucasians, from a 42% reduction in Pakistani (OR 0.58; 0.53 to 0.63) to a 59% increase in Caribbean (OR 1.59; 1.46 to 1.75). Greater

social deprivation and lower comorbidity score were associated with a higher risk of admission for hypoglycaemia, being ORs 1.02 (1.02 to 1.03) and 0.91 (0.90 to 0.93) per unit increase of IMD–10 and Charlson score, respectively. Moderate to high heterogeneity was found across regions in the associations of risk factors (I^2 51% to 91%), particularly for Indian ethnicity, sex, and Charlson score (Figure S2 and S3).

We evidenced the same results in sensitivity analyses using different splines or defining as cases also admissions with ICD–10 codes for hypoglycaemia in any position from 2nd to 5th (3,260 admissions; Table S4).

Amongst the comorbidities related to admission for hypoglycaemia, “diabetic retinopathy” was associated with the highest absolute risk (7.2 per 1,000 admissions; 10.1 vs 2.9 per 1,000 admissions in hypoglycaemia vs non–hypoglycaemia), followed by “non–insulin–dependent diabetes with ophthalmological complications” (5.3 per 1,000), “convulsions” (5.0 per 1,000), “dementia” (4.5 per 1,000), “hypothyroidism” (4.4 per 1,000), and chronic renal failure (4.0 per 1,000) (Figure S4).

Length of hospital stay, readmission, and inpatient mortality

Length of hospital stay was shorter in case compared to control admissions (median [interquartile range]: 1 [2–7] vs 1 [4–10], respectively; $p < 0.001$) (Figure S5). Adjusted for age, sex, ethnicity, social deprivation, Charlson score, and calendar year, length of stay was 26% shorter in people admitted for hypoglycaemia (ratio length of stay hypoglycaemia vs non–hypoglycaemia admissions: 0.74; 95% CI: 0.71 to 0.77); there was high heterogeneity across regions (I^2 94%; 92 to 96), with the highest and lowest differences for London (33% shorter) and West Midlands (19% shorter), respectively (Figure 3).

Readmission risk for hypoglycaemia was higher compared to readmission for any–cause in control admissions (Figure 3). The overall OR was 1.65 (95% CI: 1.55 to 1.76) with high heterogeneity

across regions (I^2 88%; 79 to 93); the risk was lowest for East Midlands (1.51; 1.40 to 1.63) and highest for London (OR 1.93; 1.82 to 2.05).

The risk of inpatient mortality differed significantly in relation to the main reason for hospital admission (i.e., first ICD–10 code) in controls; Figure 4 depicts the odds of mortality for hypoglycaemia admissions vs the twenty most common reasons for hospitalisation in control admissions (35.2% of all control admissions; Table S3). While “angina pectoris”, “chest pain”, “atrial fibrillation/flutter”, or “unstable angina” were associated with a lower risk of inpatient mortality (ORs from 0.14 to 0.54) compared to hypoglycaemia, no differences in mortality were found for admissions of subjects with “insulin–dependent or non–insulin–dependent diabetes without complications”, “syncope/collapse”, “cellulitis of limb”, or “insulin–dependent diabetes mellitus with ketoacidosis”. Conversely, the mortality risk was significantly higher for “acute lower respiratory infection”, “congestive heart failure”, “acute myocardial infarction”, “acute renal failure”, or “pneumonia” (ORs from 1.64 to 7.82). Moderate to high heterogeneity was found across regions for cause–specific mortality (I^2 20% to 76%).

Sensitivity analysis including cases with 2nd to 5th ICD–10 codes for hypoglycaemia yielded the same results for the three outcomes.

Supplementary analysis: age and risk of admission by diabetes type

After the exclusion of participants with inconsistent coding of diabetes type (details of sample definition are reported in the Supplementary Appendix, Table S5, and Figure S6), 338,199 participants contributing to 387,780 admissions were included in analyses; characteristics of admissions by diabetes type are reported in Table S6. In subject with “insulin–dependent diabetes mellitus”, the relationship between age and risk of admissions for hypoglycaemia, adjusted for sex, ethnicity, IMD–10, Charlson score, and calendar year, evidenced a U–shaped curve with higher risk

in patients younger than 20 and older than 70 years (Figure S7). Conversely, in patients with “non–insulin–dependent diabetes” the risk was progressively higher only in subjects older than 60 years.

DISCUSSION

Principal findings

In this analysis, we identified and estimated the association of sociodemographic risk factors with hospitalisation for hypoglycaemia and subsequent outcomes in a large sample of subject with diabetes. Using national data, we selected all admissions reporting hypoglycaemia as the first ICD–10 code (i.e., primary diagnosis) and a random sample of admissions for any other cause in people with diabetes to quantify the impact of several individual factors on the risk of admission for hypoglycaemia as well as to assess differences on three key outcomes, namely hospital length of stay, readmissions, and inpatient mortality. Our results indicated that, among hospital-admitted individuals with diabetes, age, social deprivation, multimorbidity (particularly visual impairment, dementia, and renal failure), and ethnicity were important determinants of admission for hypoglycaemia; readmission for hypoglycaemia was greater than the risk of readmission for any other cause in subjects admitted not for hypoglycaemia; time to discharge and mortality were significantly lower following hospitalisation for hypoglycaemia; and differences for length of stay, readmission, and mortality comparing hypoglycaemia vs non–hypoglycaemia varied across regions.

Results in the context of available evidence

Previous observational analyses have investigated risk factors for severe hypoglycaemia or emergency visit/hospital admission for hypoglycaemia. Using the UK–based General Practice Research Database, Bruderer et al. identified retrospectively risk factors for severe hypoglycaemia with a nested case–control design including 690 participants with type 2 diabetes and hypoglycaemia and a selection of 6,900 controls without any recorded hypoglycaemic event [14]. They found an increased risk of severe hypoglycaemia (defined as an episode requiring a third part assistance, followed by coma, or glucose level <3.0 mmol/l followed by emergency admission to hospital or by death within 30 days) in older people with renal failure, cognitive impairment/dementia, or treated

with insulin or sulphonylurea. Using a similar database in Germany, Kostev et al. identified younger age, diabetes duration, and several diseases (renal failure, autonomic neuropathy, dementia, and depression) as risk factors for 3,221 ICD–10 defined hypoglycaemic events in ~33,000 insulin–treated subjects with type 2 diabetes [15]. Other observational studies, as well as post–hoc analyses of randomised control trials, have confirmed the relevance of age, comorbidities, and use of insulin and secretagogues as risk factors for emergency visit/hospital admission for hypoglycaemia [16–20].

Given the increased risk of hypoglycaemia in younger subjects with type 1 diabetes and the limited and conflicting epidemiological evidence about age and hospital admission for hypoglycaemia (with studies including only age–specific groups of patients), in our study we modelled age to ascertain whether its relationship with hospitalisation was non–linear. Compared to 60 years old, we observed a progressive increase in relative risk for younger and older subjects; the shape of association, of note, accounted for other potential risk factors and was robust to statistical modelling. This relationship was further investigated in a supplementary analysis stratified by diabetes type. Within the limitations of diabetes definition in HES, we noticed a higher risk of admissions in both younger and older patients with “insulin–dependent” diabetes while for “non–insulin–dependent” diabetes the risk increased only in patients older than 60 years. It is plausible that younger, healthier type 1 diabetes patients without comorbidities have an increased risk of admissions for hypoglycaemia due to insulin therapy; in contrast, older type 2 diabetes patients not on insulin therapy and with more comorbidities are more likely to be admitted for other causes (as also suggested by the higher Charlson score in control admissions). Importantly, the absolute number of admissions was much greater in older than younger patients: our data indicate that subjects older than 70 years contribute by ~60% to the overall number of hospitalisations (i.e. ~5,900 per year).

We also investigated the impact of specific comorbidities on the risk of admission for hypoglycaemia. We found that retinopathy is roughly 3–time more common in subjects admitted for hypoglycaemia, with an absolute difference of 0.7% (1% and 0.3% in hypoglycaemia *vs* non–

hypoglycaemia, respectively). “Ophthalmological complications” in “insulin-dependent” or “non-insulin-dependent” diabetes were also amongst the most common co-reported ICD codes, along with chronic kidney failure and dementia. While suboptimal glucose control could be associated with both a higher prevalence of comorbidities and a greater risk of hospital admissions for hypoglycaemia, nonetheless the reduced clearance of several glucose-lowering drugs in patients with kidney failure and the higher risk of incorrect administration of insulin doses in patients with dementia or retinopathy may also explain these findings.

Our results also showed important differences in the risk of admissions according to ethnicity. Compared to Caucasians, people of Pakistani, Bangladeshi, and Indian ethnicity had lower whilst Caribbeans had a higher risk of hospitalisation for hypoglycaemia. Observational studies and a post-hoc analysis of the ACCORD randomised controlled trial have reported an increased rate of emergency department visits or admissions for hypoglycaemia in black (African-American race) compared to white patients in North American populations [16, 21, 22]. In England, a previous observational study found ~2.5-time higher risk of diabetes-related hospitalisation (first or second ICD-10 codes E10–E14 using 2010–11 HES data) comparing South Asians to White British [23]. Although the relationship between south Asian ethnicity and risk of type 2 diabetes, glucose control, and vascular complications is currently of great interest [24], to our knowledge this is the first study that explored ethnic differences for admissions for hypoglycaemia using national-level data in England. Multiple clinical, socioeconomic, or cultural factors could help elucidate differences across ethnicities. Previous data have suggested less aggressive management of glucose in south Asian patients – Pakistani, Indian, and Bangladeshi in this study – compared to white Europeans [25, 26], and this could explain the lower rate of admissions evidenced in this study. Furthermore, the severity of comorbidities associated with hypoglycaemia may differ across ethnicities [24]; though we adjusted for comorbidities using the Charlson score, this index does not take into account disease severity. Socioeconomic and cultural factors also interplay with ethnicity in determining the risk of

hypoglycaemia [23]. Studies have shown greater concerns in south Asians about insulin initiation and hypoglycaemia [27], lower adherence to oral glucose-lowering drugs [28], fewer prescription of insulin therapy [29, 30], and reduced awareness of diabetes and its complications [31]. All these factors could result in worse glucose control and potentially explain the lower risk of hypoglycaemia. However, our findings should be considered in the context of previous evidence indicating differences in hospital admissions across ethnicities for several other medical conditions and health-related outcomes [32, 33]. While adding new insights over ethnicity-glucose control relationship, we deem our results further underline the importance of conducting studies to elucidate the specific contribution of clinical, socioeconomic, and cultural factors on the risk of severe hypoglycaemia and healthcare resource utilisation in different ethnicities.

In contrast with our findings, in a small retrospective audit including ~1,500 subjects with diabetes Tan et al. showed a longer hospital stay and an overall higher inpatient mortality in patients admitted for hypoglycaemia *vs* non-hypoglycaemia (10.3 *vs* 7.3 days and 14.5% *vs* 5.2%, respectively) [11]. The paucity of other comparative assessments for length of stay, mortality, and readmission limited a broader comparison with our data. This is particularly important for readmissions because we evidenced a 65% higher probability of readmission in people admitted for hypoglycaemia; the identification of risk factors for readmissions would therefore significantly impact on the overall number of hospitalisation for hypoglycaemia and associated healthcare costs.

We also noticed heterogeneity across regions of England in the association of risk factors with hospitalisation for hypoglycaemia and for the outcomes length of stay, readmission, and mortality. While heterogeneity was moderate to high for ethnicity, it was considerably higher ($I^2 > 75\%$) for sex, Charlson score, length of stay, and readmissions; regional differences in mortality risk, on the other hand, were largely dependent on the reason of control admissions. Heterogeneity may be related to differences in clinical unmeasured factors or to variations in nonclinical aspects associated with admissions and outcomes. Of note, regional variations have been reported for several other health

indicators and should be interpreted in conjunction with the results on ethnicity and social deprivation [34, 35].

Strengths and weaknesses of the study

A major strength of this research is the use of detailed data on all hospital admissions for hypoglycaemia in England over a period of 10 years. This information enabled us to estimate risk factors for hypoglycaemia admissions and subsequent outcomes at national level and to investigate regional differences. This research also has limitations. First, HES data are routinely collected for administrative rather than research purposes; as such, there is some potential for inaccuracies in data collection and accuracy. This is particularly relevant for the definition of diabetes type; further studies are required to detail the relationship between age and other risk factors with admission for hypoglycaemia in type 1 and type 2 diabetes. Second, information on other important risk factors are not available in HES. Glucose-lowering therapies might confound the association between admissions for hypoglycaemia and factors included in this analysis: compared to other treatments, insulin therapy is more common in older participants with long disease duration and comorbidities and is also associated with a higher risk of hypoglycaemia. On the other hand, glucose-lowering therapies could be more relevant as potential confounder for the outcomes admission/readmission and less important for inpatient mortality and length of hospital stay (which are more likely related to age and comorbidity index). Third, we compared inpatient mortality and not short- or long-term mortality after discharge. Lastly, in subjects admitted for hypoglycaemia, we investigated readmissions only for hypoglycaemia.

Conclusions

As hospital admissions for hypoglycaemia constitute a significant burden for patients with diabetes and for the healthcare system, the identification of potential risk factors is an important exercise

which helps identifying at-risk groups and implement appropriate strategies. Further clinical and socio-demographic studies are required to confirm and expand our findings, particularly the large ethnicity differences.

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Data access: FZ and GH had full access to the dataset under the terms of the Hospital Episode Statistics Data Re–Use Agreement.

Competing interests: KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi–Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi–Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme. KK has received funds for research, honoraria for speaking at meetings and has served on advisory boards for Lilly, Sanofi–Aventis, Merck Sharp & Dohme and Novo Nordisk.

MJD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi–Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi–Aventis and Lilly.

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FIGURE LEGENDS

Figure 1: Age-specific odds ratios of admission for hypoglycaemia

Legend: Estimates, adjusted for sex, ethnicity, IMD-10, Charlson score, and calendar year, are reported comparing admissions for hypoglycaemia vs non-hypoglycaemia. The line indicates age-specific odds ratios relative to age 60 years old, with 95% CI (shadow)

Figure 2: Risk factors for admission for hypoglycaemia

Legend: Estimates adjusted for risk factors shown plus age and calendar year. Odds ratios reported per unit increase of IMD-10 (more deprived) and Charlson score (greater multimorbidity)

Figure 3: Length of stay and risk of readmission comparing admissions for hypoglycaemia vs non-hypoglycaemia, by region

Legend: Estimates, adjusted for age, sex, ethnicity, IMD-10, Charlson score, and calendar year, are reported comparing admissions for hypoglycaemia vs non-hypoglycaemia. Overall, hospital stay was 26% shorter and risk of readmissions 65% higher in people admitted for hypoglycaemia

Figure 4: Risk of inpatient mortality comparing hypoglycaemia to other common reasons of admission

Legend: Estimates, adjusted for age, sex, ethnicity, IMD-10, Charlson score, and calendar year, are reported comparing admissions for hypoglycaemia (reference, 1) vs the twenty most common reasons of admission (1st ICD code). For hypoglycaemia there were 3,106 deaths in 101,353 admissions. IDDM: Insulin-dependent diabetes mellitus; NIDDM: Non-insulin-dependent diabetes mellitus; COPD: Chronic obstructive pulmonary disease