

Running title: Hypoglycaemia in database studies

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In this issue of DOM, Zaccardi et al. present an analysis of hypoglycaemia-related hospitalizations in the Hospital Episodes Statistics (HES) administrative database of the English National Health Service. [1] Notable strengths of the work include a large sample size involving more than 100 000 cases of hypoglycaemia, and nationwide capture spanning a duration of ten years. Key conclusions include the possibility of a U-shaped relationship between risk of hypoglycaemia and age, as well as possible

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associations between social deprivation and ethnicity with greater risk of hypoglycaemia.

However, there are particular challenges in using routine administrative or healthcare databases to evaluate risk factors for hypoglycaemia, and we must recognize the major limitations that affect the interpretation of such analyses. Researchers aiming to determine the incidence, predisposing factors and consequences of hypoglycaemia need to overcome hurdles in identifying sufficiently comprehensive and reliable datasets. However, some databases may have been designed for the primary purpose of supporting administrative activity and/or insurance reimbursement, without any specific steps taken to accurately capture detailed clinical data in a bespoke manner.

[2] Diagnostic criteria are often not explicit or consistent, and some form of subjectivity is inherent in the coding of events and procedures.

A major obstacle to accurate determination of hypoglycaemia incidence is the diversity in signs and symptoms of hypoglycaemia, some of which may or may not come to medical attention – for instance, episodes that are self-managed will not be captured in healthcare records. Even where medical attention is sought, the setting and nature of intervention varies considerably, from paramedics treating at the patient's own home to emergency department care with, or without subsequent hospitalization. This means that the hypoglycaemic events may end up being captured on certain clinical databases, but not other ones – e.g. the patient discharged from the Emergency Department would not be captured in the admissions database.

Detailed assessment of the predisposing factors for hypoglycaemia also poses serious challenges. Susceptibility to hypoglycaemia is determined by a complex intermix of factors including type of glucose lowering therapy (particularly insulin), glycosylated haemoglobin concentrations, comorbid conditions such as renal impairment, cognitive

decline, and age. [3, 4] Multivariable analysis based on reliably measured data is needed when trying to determine the extent to which certain covariates may or may not independently contribute to risk of hypoglycaemia. The comprehensiveness and accuracy of the recorded clinical data may not be sufficient to allow evaluation of all potentially relevant variables.

Hospital-based administrative datasets, for the reasons stated above, may therefore not be the best sources for evaluating differences in incidence and risk factors for hypoglycaemia. These databases only contain codes of events within an episode that took place within a single healthcare setting. Absence of longitudinal data on past medical and treatment history from primary care setting is a serious limitation. For instance, the absence of key parameters (such as insulin use, trends in glycosylated haemoglobin and renal function) in the HES database, could lead to confounded findings in the multivariable analysis regarding the extent to which factors such as age, social deprivation and ethnicity independently contribute to risk of hypoglycaemia. Any evaluation, for instance, of risk of hypoglycaemia according to social deprivation, is potentially confounded by whether certain socially deprived groups have a higher prevalence of severe renal impairment, or whether there are greater number of insulin users in that particular group.

Equally, the analysis of inpatient mortality within hospital administrative databases may be restricted to all-cause mortality i.e. HES records the cause of admission, but not the actual cause of death. The absence of linkage to manual or electronic prescribing systems means that hospital databases may not provide details of what treatments the patient received during their inpatient episode. This is particularly relevant when evaluating inpatient stay and mortality in patients admitted with

hypoglycaemia because the cause and subsequent complications of the hypoglycaemic event may have stemmed from underlying severe liver/renal failure, or overwhelming sepsis.

Whilst we recognize that healthcare administrative databases may appear to be an attractive, easily accessible source of data on large numbers of patients, we are also acutely aware of key limitations relating to depth and accuracy of clinical data, and the inability to capture events longitudinally outside of that particular database. There are a number of ways to overcome these challenges though, with record linkage being one of the most promising options. For instance, the UK Clinical Practice Research Datalink (CPRD) allows linkage to the HES Inpatient and Outpatient Database, as well as HES for emergency care. [5] This would allow good capture of baseline characteristics of the patients and their primary care prescriptions (through CPRD), whilst hospital and emergency care attendances would be available through HES. There is also linkage between CPRD and certified cause of death through the Office of National Statistics, UK. Use of all these linked datasets potentially provides a much more comprehensive picture of the patient's healthcare journey, particularly with events such as hypoglycaemia which can manifest in any setting and with unpredictable long-term consequences.

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- [1] Zaccardi F, Webb DR, Davies MJ. Risk factors and outcome differences in hypoglycaemia-related hospital admissions A case-control study in England. 2017:
- [2] Loke YK. Use of databases for clinical research. Arch Dis Child. 2014; **99**: 587-589
- [3] Bloomfield HE, Greer N, Newman D, *et al.* VA Evidence-based Synthesis Program Reports. Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes - A Systematic Review of the Evidence. Washington (DC): Department of Veterans Affairs, 2012
- [4] Mattishent K, Loke YK. Bi-directional interaction between hypoglycaemia and cognitive impairment in elderly patients treated with glucose-lowering agents: a systematic review and meta-analysis. Diabetes Obes Metab. 2016; **18**: 135-141
- [5] Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). International Journal of Epidemiology. 2015; **44**: 827-836