The effect of hypoglycaemia during hospital admission on health-related outcomes for people with diabetes: A systematic review and meta-analysis

Short title: Effect of inpatient hypoglycaemia: systematic review and meta-analysis

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Novelty statement:

- Heterogeneity of populations and definitions of hypoglycaemia are a significant challenge in synthesising evidence from previously published studies
- Hypoglycaemia events, including those considered non-severe are associated with an increased length of hospital stay and increased risk of inpatient mortality
- Inpatient hypoglycaemia is a marker for clinical deterioration and potential increased risk for adverse outcomes
- Glucose measurements could aid the identification of patients at risk of poor health-related outcomes

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Abstract

Aims: To assess the health-related outcomes of hypoglycaemia for people with diabetes admitted to hospital; specifically, hospital length of stay and mortality.

Methods: We conducted a systematic review and meta-analysis of studies relating to inpatient hypoglycaemia (<4 mmol/L) for hospitalised adults (≥16 years) with diabetes reporting the primary outcomes of interest, hospital length of stay or mortality. Final papers for inclusion were reviewed in duplicate and the adjusted results of each were pooled, using a random effects model then undergoing further prespecified subgroup analysis.

Results: 15 studies were included in the meta-analysis. The pooled mean difference in length of stay for ward-based inpatients exposed to hypoglycaemia was 4.1 days longer (95% confidence interval [CI], 2.36-5.79; I^2 = 99%) compared to inpatients without hypoglycaemia. This association remained robust across the pre-specified subgroup analyses. The pooled relative risk (RR) of in-hospital mortality was greater for inpatients exposed to hypoglycaemia 2.09 (95% CI, 1.64 to 2.67; I^2 = 94%, n=7 studies) but not in intensive care unit mortality RR 0.75 (0.49 to 1.16; I^2 =0%, n=2 studies).

Conclusion: There is an association between inpatient hypoglycaemia and longer length of stay and greater in-hospital mortality. Studies examining this association were heterogenous in terms of both clinical populations and effect size, but the overall direction of the association was consistent. Therefore, glucose concentration should be considered a potential tool to aid the identification of patients at risk of poor health-related outcomes.

Key words: Diabetes, Hypoglycaemia, hospital in-patients, inpatient, meta-analysis

Introduction

One in six NHS hospitals beds, across all specialties, is occupied by someone with diabetes [1]. The National Inpatient Diabetes Audit reported that among 15,774 hospitalised people with diabetes in over 200 hospitals, patients only achieved good glycaemic control on less than half of their inpatient days [2]. Additionally, approximately 20% of inpatients with insulin treated diabetes experience one or more episodes of hypoglycaemia, with 8% of episodes classed as severe. Hypoglycaemia is also a common occurrence in critically unwell people without diabetes.

In 2017 the International Hypoglycaemia Study Group defined hypoglycaemia in clinical trials as <3.0 mmol/L with a level of 3.0 to 3.9mmol/L redefined as an alert level. They also reported in people with diabetes the counterregulatory response to hypoglycaemia will differ dependent on their individual glucose control [3]. It remains common practice however, for a glucose level of less than 4 mmol/L to trigger hypoglycaemia treatments in hospital [4].

There are several factors associated with the increased risk of in-patient hypoglycaemia for people with diabetes. These may relate to physiology changes, changes in pharmacological treatments, change in the environment and inappropriate diabetes management. Physiological and pharmacological factors include acute kidney injury, liver failure, sepsis and reduction in medications known to increase glucose levels such as corticosteroids and polypharmacy. Changes in the environment increase hypoglycaemia risk through factors such as the limited availability of food, long fasting time from evening meal to breakfast and unexpected deviations in hospital care. Inappropriate diabetes management includes overuse of variable rate intravenous insulin infusion, prescribing errors and drug administration errors [5,6]. Despite the potential morbidity and known risk

factors for hypoglycaemia [7], measures to counteract these risks in hospital are not routinely taken.

Extant studies examining the effect of inpatient hypoglycaemia have generally found negative clinical outcomes, but with estimates of varying precision and from a range of clinical populations [8-24]. Therefore, we performed a systematic review and meta-analysis to investigate to what extent inpatient hypoglycaemia influences hospital length of stay and mortality. This review focuses on people with diabetes who were exposed to hypoglycaemia during their hospital admission.

Research design and methods

In accordance with our published protocol (PROSPERO CRD42017062611), we performed a systematic review and meta-analysis. Studies were included if they met all of the following criteria: participants were adults (≥ 16 years) and had a diagnosis of diabetes (or data from study participants with diabetes could be extracted separately); the exposed group experienced hypoglycaemia (<4.0 mmol/L or equivalent hospital coding) and was compared against a control group without hypoglycaemia; and the study outcomes included one or both of the primary outcomes for this systematic review (length of stay or mortality). Papers were excluded if study samples included participants who were admitted with hypoglycaemia, included paediatric or pregnant populations, were based in a primary care or emergency department setting or if the study did not report either outcome of interest or a qualitative research design was used. Reporting is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. A multidisciplinary panel of academic and clinical experts was formed. This panel determined the review protocol and contributed to various aspects of the review.

Data Sources and Search Strategy

The following databases were searched for all available dates: MEDLINE (Ovid), EMBASE, CINAHL Complete, Scopus and Web of Science, clinicaltrials.gov, UK Clinical trials, gateway (current and archived), Open Grey, NHS Evidence, ProQuest UK/Ireland, ProQuest International, Prospero and the Cochrane databases. These databases where chosen as they hold papers on healthcare related research from various professional perspectives [26,27]. The first database search was undertaken on the 28th June 2017 and an updated search on MEDLINE (Ovid), EMBASE, CINAHL Complete, Scopus and Web of Science was undertaken on the 6th June 2018 using the same search terms. Details of the search terms used are provided (Appendix 1). Both searches were undertaken through the website of the host university using the same search strategy and databases [28].

The MEDLINE (Ovid), EMBASE, CINAHL Complete, Scopus and Web of Science searches were carried out by the lead author and independently by an information specialist on the same day. All searches were limited to the English language. Reference management was carried out using Mendeley.

Study selection

All titles and abstracts were assessed independently and in duplicate to identify articles requiring full text review against the predefined inclusion criteria. Papers found through grey literature searching were assessed by the first author (AL). Eligible citations identified after title and abstract review were all then full text reviewed by two people. Reasons for exclusion were recorded. Any disagreements between reviewers were resolved by consensus and in consultation with the expert panel. Review of the reference

lists of the citations for full-text review was also undertaken (by AL) to identify additional relevant papers.

Data extraction

Data from included studies were extracted using prespecified data extraction forms. Extracted data included study demographics and design, in-hospital location, diagnostic criteria for hypoglycaemia, sample size and outcomes reported. Where reported, adjusted findings were used. Hypoglycaemia definitions were grouped for analyses in line with the consensus recommendation made by the international hypoglycaemic group (non-severe: ≥3.0 mmol/L and <4.0 mmol/L or serious: <3.0 mmol/L) [3]. For studies with missing data or inconsistencies authors were contacted. If the data could not be retrieved or queries resolved the citation was excluded from the meta-analysis. The standard deviation was not reported for two studies therefore it was imputed based on the mean of the studies reporting a similar mean. These publications were removed during sensitivity analysis [29]. Record management was carried out using Microsoft Excel.

Data Synthesis

The primary outcome was hospital length of stay and all-cause mortality. Data were pooled into relative risk (RRs) or mean difference with 95% CI for dichotomous outcomes and continuous outcomes, respectively. Meta-analysis was performed using random effects models, applying the DerSimonian and Laird statistical method [30].

A prespecified analysis was undertaken stratified by hospital location (intensive care unit (ICU), medical ward and/or other speciality areas, not specified), research methodology, hypoglycaemia definition group, removal of outliers, removal of poor-quality papers, prospective cohort study design, and time point of reported outcomes (in hospital mortality

vs. post discharge mortality). Statistical heterogeneity was assessed through the I^2 test for heterogeneity. Regression tests for analysis and publication bias were not completed as there were less than 10 papers overall for publication bias or per covariate in meta-regression tests [31,32]. Small study effect was examined using funnel plots. Analysis was conducted using RevMan version 5.3.

Quality Assessment

Studies were reviewed to determine whether the cohort observed was representative of the study population and whether there was risk of bias in the recruitment process or identification of the exposure to hypoglycaemia [33]. Bias and methodological assessment was completed by two reviewers (AL and CB) using an adapted version of the Newcastle Ottawa Scale [34]. The Newcastle Ottawa scale rates eight items relevant to cohort studies design: representativeness of cohort, selection of non-exposed cohort, ascertainment of exposure, demonstration of no exposure at admission, comparability of cohorts, assessment of outcome, sufficient length of follow-up and adequacy of follow-up. Each study was then given a total score equating to a rating of poor, fair or good quality. The results were compared, and disagreements resolved through consensus [35].

Results

A total of 10,374 papers were identified, 8,401 through database searches and 1,973 through other sources. Once duplicates were removed 7,290 remained and were reviewed by title and abstract for eligibility. 7,195 studies were excluded based on the inclusion criteria leaving 95 for full review. A further 72 studies were excluded following the full text review leaving 23 to be included. Another six were excluded as the data required for analysis could not be extracted. For length of stay, the reason for exclusion was typically

because a mean and standard deviation could not be extracted. For mortality, the most common reason found for exclusion was because the data for people with diabetes could not be separated from those without diabetes. Of the 17 remaining studies, three papers were by the same author Krinsley et al [8-10] and a combined dataset was kindly provided by the lead author to prevent duplication of analysis. This resulted in 15 eligible studies [8-24], (Figure 1).

Table 1: Eligible studies included in the meta-analysis

Author, Year	Country	Hospital location	Study Design	Total patients or admissions	Total exposed to hypo	People with diabetes (%)	T1DM	T2DM	Treated with insulin (%)	Treated with oral agents (%)	Non exposed group	Adjustments during analysis	Hypo definition (mmol/L)	Outcome
Gomez-Huelgas, 2015	Spain	N/S	RCS	309,020	154,510	100%	N/S¥	291,827	N/S	N/S	MP	Age, sex, type of diabetes, readmission, CCI, primary or secondary hypoglycaemia	ICD code	↑LOS, ↑ In-hospital mortality
McEwan, 2015,	UK	N/S	RCS	2,158	1,079	100%	424	1,734	100%	0%	MP	Age, sex, type of diabetes, use of medication, BMI, HbA1c, smoking, geographical region and CCI	ICD code	↑LOS, ↑In-hospital mortality*
Curkendall, 2009,	USA	N/S	RCS	103,813	8,234	100%	5261¥	87,610¥	25.5%	N/S	NM	Age, sex, type of diabetes, race, specific complications, events and conditions during hospitalization¥, CCI, insulin use, hospital characteristics and clinically plausible interactions	< 3.9	↑LOS, ↑In-hospital mortality
Geremakis, 2014,	USA	N/S	CCS	8952	2,510	100%	N/S	N/S	N/S	N/S	CC	Ethnicity, admitting hospital, CCI, surgery, fungal infection, antipsychotics, pulmonary hypertension, antidepressants, beta adrenergic, cephalosporin, antibiotics	<2.2	↑LOS
The NICE-SUGAR Study Investigators, 2012,	USA	ICU	SaRCT	6,026	643	20%	N/S	N/S	N/S	N/S	NM	Age, sex, APACHE II score, BMI, blood glucose, postoperative status, sepsis, trauma, diabetes, prior insulin or steroid treatment, cardiac failure, intensive vs. conventional insulin	≤3.9	↑ Mortality within 90 days

Krinsley, 2017, 2011, 2007~	USA	ICU	SaRCT	2,786‡	683	100%	N/S	N/S	N/S	N/S	NM	Age, sex, APACHE II score, APACHE III score, mechanical ventilation	< 3.9	↑In-hospital mortality
Sechterbergr, 2013	Netherlands	ICU	RCS	10,320.	57	16%	N/S	N/S	98%	N/S	NM	Age, sex, APACHE II score, hypoglycaemia severity, cardiothoracic surgery, glucose variability, mean glucose, glucose levels ≤4.7 mmol/L	≤2.2	↑ICU mortality
Arabi, 2009	Saudi Arabia	ICU	NC	523	46	40%	N/S	N/S	87%	N/S	NM	Age, sex, BMI, postoperative status, APACHE II score, diabetes, admission glucose, mechanically ventilated, vasopressor, sepsis, creatinine, dialysis/ filtration, intensive insulin	≤2.2	→ ICU mortality
Turchin, 2009	USA	General ward	RCS	4,368 admissions	338 admissions	100%	N/S	N/S	61.8% received insulin, OHA or both		NM for mortality. MP for LOS	Age, sex, ethnicity, health insurance, weighted mean daily glucose, LOS based on DRG and modified CCI	≤2.8	↑LOS ↑In-hospital mortality
Ong, 2015	Singapore	General Ward	RCS	288	54	100%	N/S	N/S	91% received insulin, OHA or both		NM	Age, sex, ethnicity, BMI, HbA1c, number of comorbidities, systolic BP, admitting specialty, diabetes treatment, steroids and IV dextrose	<4.0	↑LOS
Borzi, 2016	Italy	General Ward	SaCSS	3,167	385	100%	0	3167	N/S	N/S	NM	Age, sex, BMI, concomitant disease, insulin treatment, serum creatinine, HbA1c, fasting glucose and number of treatments other than diabetes	<3.9	↑LOS ↑In-hospital mortality

Nirantharakuma 2012	UK	General Ward	RCS	6,374 admissions	648 admissions	100%	N/S	N/S	25%	N/S	NM	Age, sex, ethnicity, deprivation, admission type, insulin use, modified CCI	< 3.9	↑In-hospital mortality, ↑ LOS†
Kim, 2014	USA	General Ward	RCS	1,276 admissions	313	99%	63¥	1198¥	0%	100%	NM	Age, sex, ethnicity, insulin use, CCI	≤3.9	↑LOS
Bouchi, 2011	USA	General Ward	RCS	31,970‡	1,717	34%	N/S	N/S	19%	11%	NM	Age, sex, ethnicity, co-morbidities, number glucose determinators, diabetes treatment	≤3.9	↑In-hospital mortality, ↑LOS
Mellbin, 2008	Sweden	Cardiac specialit y	SaRCT	1,253	153	100%	0	1253	N/S	N/S	NM	Age, sex, smoking status, previous myocardial infarction & coronary interventions, cardiac failure, pharmacological treatment, creatinine, diabetes duration, blood glucose before and during admission	<3.0	→Total mortality (median follow up 2.1 years)

*Applicable only to people with diabetes. (not included in meta-analysis as data not available) ‡Data provided by author, † (not in meta-analyses as only median data reported); ¥remainder had unknown or undisclosed type of diabetes; T1DM – Type 1 diabetes; T2DM – Type 2 diabetes; N/S – Not specified; UK – United Kingdom; USA – United States of America; ICU – Intensive care unit; RCS – Retrospective cohort study; CCS – Case controlled study; SaRCT - Sub-analysis of randomised control trial; NC - Nested cohort within a randomised control trial; SaCSS - Sub-analysis of two cross sectional studies; OHA – Oral hypoglycaemic agents; MP – Matched patients; NM – Non -matched; CC – Case controlled; CCI - Charlson comorbidity score; DRG – Diagnostic related group; LOS – Length of stay;

Study Characteristics

The characteristics of the 15 included studies are shown on Table 1. The hospital locations included the general ward (n=6) intensive care unit (n=4), not specified (n=4) and a specialty cardiac ward (n=1). Studies were published between 2009 and 2016 and their designs included observational studies (n=9), sub-analysis of a randomised controlled trial (n=3), nested cohort within a randomised control trial (n=1), sub analysis of a cross sectional study (n=1) and a case-controlled study (n=1). Geographical locations included the United States of America (n=7), United Kingdom (n=2), and one each from Spain, the Netherlands, Saudi Arabia, Singapore, Italy and Sweden. Most were single centre studies with a mean sample size of 32,788 (ranging from 288 to 300,020), with a mean of 11,425 people with diabetes exposed to hypoglycaemia. All studies adjusted for age, sex and comorbidities. Eight studies adjusted for at least one other patient demographic such as socio-economic status, ethnicity, health insurance status or education level.

Quality Assessment

Of the 15 studies reviewed, the ascertainment of hypoglycaemia exposure and selection of the non-exposed cohort were clearly reported. Many studies that would otherwise have scored highly were rated poor as it was not explicitly stated if the population was or was not admitted with hypoglycaemia nor the exact follow-up duration. We recognise that it is likely due to many of the included studies not being published with their suitability for subsequent systematic review in mind. All papers reported the selection of the non-exposed cohort, method of ascertainment of exposure and used record linkage for assessment of outcome.

Association between inpatient hypoglycaemia and length of hospital stay outside intensive care

The overall pooled mean difference of the nine studies reporting length of stay outcomes [11-14,18-20, 22, 23] suggests that people with diabetes, who experienced at least one episode of hypoglycaemia during their admission, had an increased length of hospital stay by a mean of 4.08 days (95% CI, 2.36 to 5.79, n=9 studies) (Figure 2a). This statistically significant association held for all sub-group analyses. While the statistical heterogeneity was very high (I^2 = 99%), all included studies demonstrated hypoglycaemia was associated with increased length of stay even when only the five papers reporting non-severe definitions of hypoglycaemia were included 4.37 (95% CI, 2.13 to 6.61, I^2 = 98%, n=5 studies)[13,19,20,22,23].

Association between inpatient hypoglycaemia and all-cause mortality by mortality timepoint

The overall pooled relative risk of in-hospital mortality from the ward based or location not specified studies [11,13,18,20,21,23,24] was 1.90 (95% CI, 1.51 to 2.39; I^2 = 93%, n=7 studies) suggesting the risk of in-hospital mortality is nearly doubled for people with diabetes exposed to hypoglycaemia. This remained significant when analysis was restricted to the two studies reporting 90 day and post discharge mortality RR 1.26 (95% CI, 1.08 to 1.47; I^2 = 0%, n=2 studies) [15,24]. However, there was no association found for the overall pooled relative risk (RR) of the two studies reporting intensive care unit mortality RR 0.75 (95% CI, 0.49 to 1.16; I^2 = 0%, n=2 studies) [16,17].

The in-hospital mortality results were obtained in the presence of substantial statistical heterogeneity (Figure 2b). This heterogeneity was reduced, and the risk further increased when only in-hospital mortality and non-severe hypoglycaemia definitions were included

RR 2.15 (CI, 1.98 to 2.33, I^2 0%, n=5 studies) [8-10,13,20,21,23] (Table 2). Of the papers looking at the association with a serious hypoglycaemia episode (<3mmol/L), only one reported in-hospital mortality [18]. Throughout the subgroup analyses the association between hypoglycaemia and mortality remained statistically significant outside of intensive care unit mortality.

Table 2 - Summary of subgroup analysis for the effect of inpatient hypoglycaemia on length of stay and mortality

Category	N= studies included	Result*	I^2
Subgroup analysis of the effect of hypoglycaemia on length of stay			
All studies	N=9	4.08 (CI, 2.36 to 5.79)	99%
Removal of papers rated as poor quality	N=4	3.59 (CI, 0.80 to 7.62)	99%
Removal of non-cohort studies	N=7	4.15 (CI, 2.11 to 6.19)	99%
Removal of studies with imputed standard deviation	N=6	3.62 (CI, 2.09 to 5.14)	98%
General ward location only	N=6	3.24 (CI, 1.01 to 5.47)	97%
Hospital location not specified only	N=4	5.08 (CI, 2.14 to 8.02)	100%
Inclusion of non-severe hypoglycaemia definitions only	N=5	4.37 (CI, 2.13 to 6.61)	98%
Inclusion of serious hypoglycaemia definitions only	N=2	2.87 (CI, -0.36 to 6.10)	98%
General ward areas only and removal of outliers	N=8	2.14 (CI, 1.30 to 2.99)	70%
General ward location and removal of papers rated as poor quality	N=2	1.63 (CI, 0.87 to 2.40)	67%
Hospital location not specified, and removal of papers rated as poor quality	N=2	5.58 (CI, 3.55 to 7.62)	97%
Subgroup analysis of the effect of hypoglycaemia on mortality			
All studies	N=11	1.69 (CI, 1.40 to 2.03)	92%
Removal of papers rated as poor quality	N=5	1.81 (CI, 1.36 to 2.42)	90%
Removal of non-cohort studies	N=4	1.62 (CI, 1.16 to 2.26)	95%
Removal of studies with imputed data	N=9	1.57 (CI, 1.29 to 1.91)	87%
In-hospital mortality only	N=7	2.09 (CI, 1.64 to 2.67)	94%
In-hospital mortality and non-severe hypoglycaemia definition	N=5	2.15 (CI, 1.98 to 2.33)	0%
Intensive care unit mortality only (all used serious hypo definitions)	N=2	0.75 (CI, 0.49 to 1.16)	0%
90-day and post discharge mortality only	N=2	1.26 (CI, 1.08 to 1.47)	0%

*Mean difference in length of stay in days or Risk Ratio (95% Confidence interval)

Small study effect

The studies reporting length of stay did not take the inverse funnel shape expected suggesting the potential presence of publication bias (Appendix 2; Figure1a). Although publication bias is less problematic in the mortality analyses, there is some potential for publication bias within the in-hospital mortality subgroup (Appendix 2; Figure1b).

Discussion

This is the first meta-analysis pooling the reported data on the effect of inpatient hypoglycaemia exposure on length of hospital stay and all-cause mortality. We found an overall positive association between hypoglycaemia and both increased length of stay and inpatient mortality outside of intensive care unit settings. No significant association was found between intensive care unit mortality and hypoglycaemia. This nonsignificant finding could reflect the frequency of blood glucose monitoring, and more responsive treatment of hypoglycaemia in intensive care compared to the general ward setting. Additionally, the patient population treated within an intensive care setting are likely to be fundamentally different to those cared for on a hospital ward. None of the included studies within the intensive care unit setting reported length of stay.

The strengths of this review include a comprehensive search strategy, designed and tested with an information specialist, reviewers' specialist diabetes knowledge and inclusion of experienced systematic review researchers. Limitations include the poor-quality rating for some studies, the presence of substantial clinical and statistical heterogeneity and the inability to be sure that patients were not admitted primarily for other diabetes related acute events other than hypoglycaemia (diabetic ketoacidosis and hyperglycaemic hyperosmolar state). We were also unable to eliminate language bias or control for

different methods of glucose measurements (capillary versus venous), glycaemic variability, causes of hypoglycaemia and inpatient hypoglycaemia management.

Despite these limitations' there are good reasons to be confident in these findings. It is supported by publications which were considered for inclusion but not eligible for the meta-analysis [36-40]. Furthermore, our findings support the statements from the American Diabetes Association [41] and the Joint British Diabetes Society [42] guidelines who report that hypoglycaemia increases risks among people with diabetes admitted to hospital.

This review has demonstrated some of the complexities and challenges associated with diabetes inpatient research. The main areas of methodological and clinical heterogeneity were the varying definitions for hypoglycaemia, different hospital locations and different research methodologies used. We attempted to address these as robustly as possible through pre-specified sensitivity testing. During acute inpatient hospital care, people from a variety of backgrounds are brought together in a hospital environment, with various presenting conditions ranging from routine surgery (e.g. cataracts, varicose vein) to life threatening emergencies (e.g. aortic aneurysm, peritonitis). Controlling for heterogeneity among the diverse population of inpatients is not possible. Even within hospital location diabetes type, individual health needs and disease severity vary greatly. This is a likely contributing factor to the substantial statistical heterogeneity. However, as the positive association between hypoglycaemia exposure and increased length of stay was largely consistent, we believe that the statistical heterogeneity represents variance in magnitude rather than the direction of the overall association.

Papers included within this review were published before the new biochemical definition of hypoglycaemia in clinical trials was published in 2017 [3]. As result, many of the studies have included in their definitions of hypoglycaemia events that would now be

considered an 'alert level'. We have attempted to address this through subgroup analysis. Contrary to expectations, the association between non-severe hypoglycaemia and length of hospital stay and in-hospital mortality remained. However, the definition of non-severe hypoglycaemia used in some studies may have included those exposed to serious hypoglycaemia as this was not an exclusion (8-10, 13, 15, 19-23).

Whether hypoglycaemia has a causal effect or is a marker of ill health is unclear and outside the scope of this review. One theory for the finding that hypoglycaemia at alert levels (≥3.0 and ≤4.0 mmol/L) within the hospital setting are associated with increased risk, is that the early associated counterregulatory response to hypoglycaemia could be harmful in acutely unwell people with diabetes. The catecholamine release in response to hypoglycaemia is less well tolerated by older patients and those with cardiac morbidities. In addition, hypoglycaemia increases both platelet aggregation and prothrombotic factors which could also contribute to increased harm [43]. While the association may not be causal, this review suggests it could be a marker for ill health or worse outcomes.

Hypoglycaemia and fear of potential hypoglycaemia remains a major barrier for healthcare professionals when supporting people with diabetes in hospital to achieve optimal glucose control [454-47]. Inadequate education and clinical knowledge about the risks associated with inpatient hypoglycaemia may be contributing to the suboptimal inpatient diabetes management documented by successive National Inpatient Diabetes Audits [48]. This review supports the need to be cautious in balancing the risks of hypoglycaemia with optimal hyperglycaemia management. To achieve better inpatient diabetes control, the gap between evidenced based medicine and clinical practice needs to be carefully considered. Consideration could be given to including hypoglycaemia on early warning systems, such as the national early warning score to raise awareness and prompt a timely review of

glucose management, or document glucose alongside other vital signs used to detect clinical deterioration [49,450].

More research is required to gain a deeper understanding of the barriers to, and potential strategies for, providing optimal inpatient diabetes care. More work is needed to update non-specialist health care professionals to implement best care for people with diabetes while admitted to hospital and support increasingly time pressured front-line hospital staff to have timely access to evidence.

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Figure legends:

Figure 1: PRISMA flow chart

Figure 2a and 2b: Mortality and Length of stay forest plots

Appendix 2; Figure 1a and 1b: The funnel plots of the mean difference and risk ratios of the primary outcomes

Figures

Figure 1: PRISMA flow chart

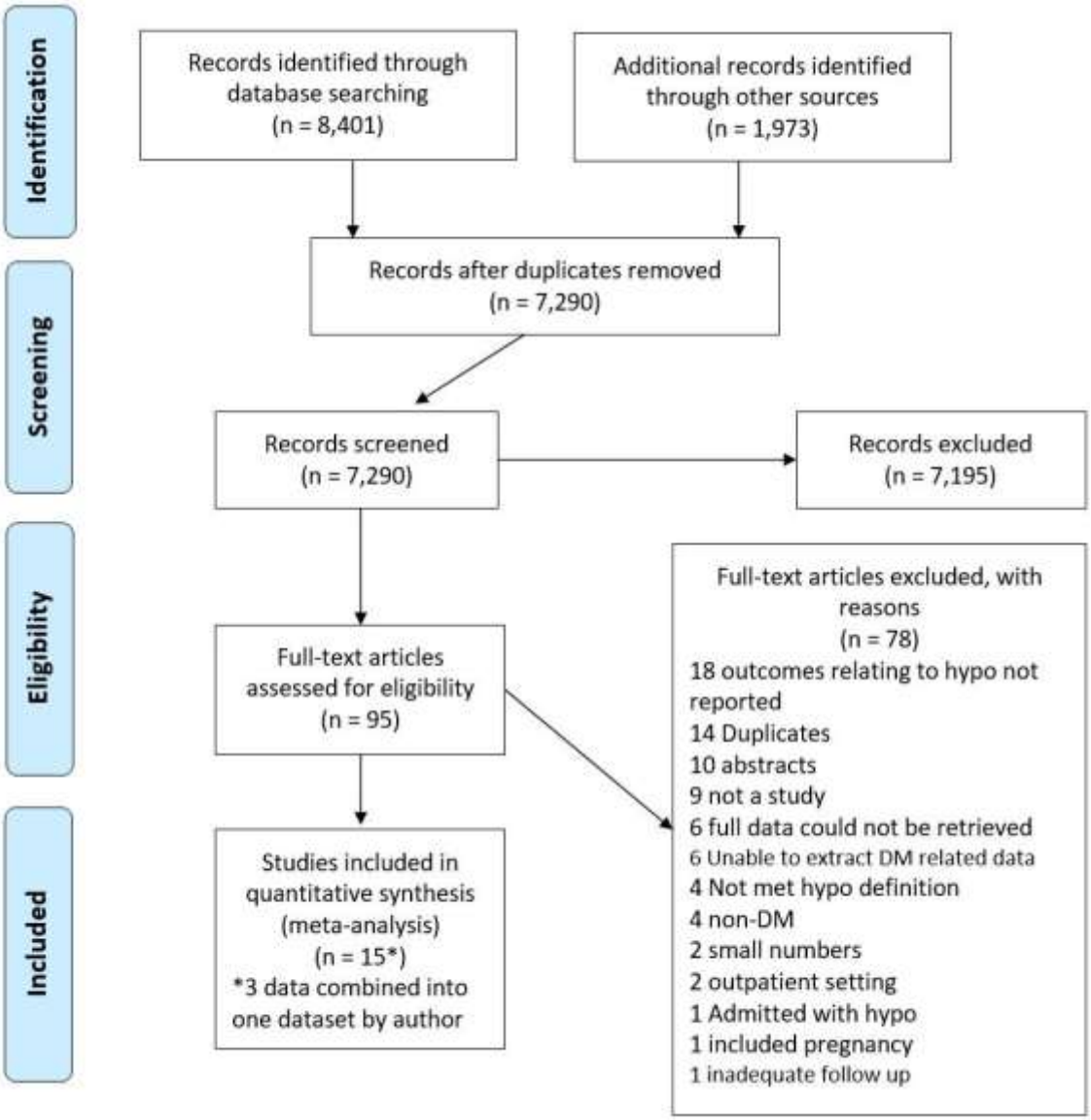


Figure 2a – In-patient hypoglycaemia and length of stay forest plot

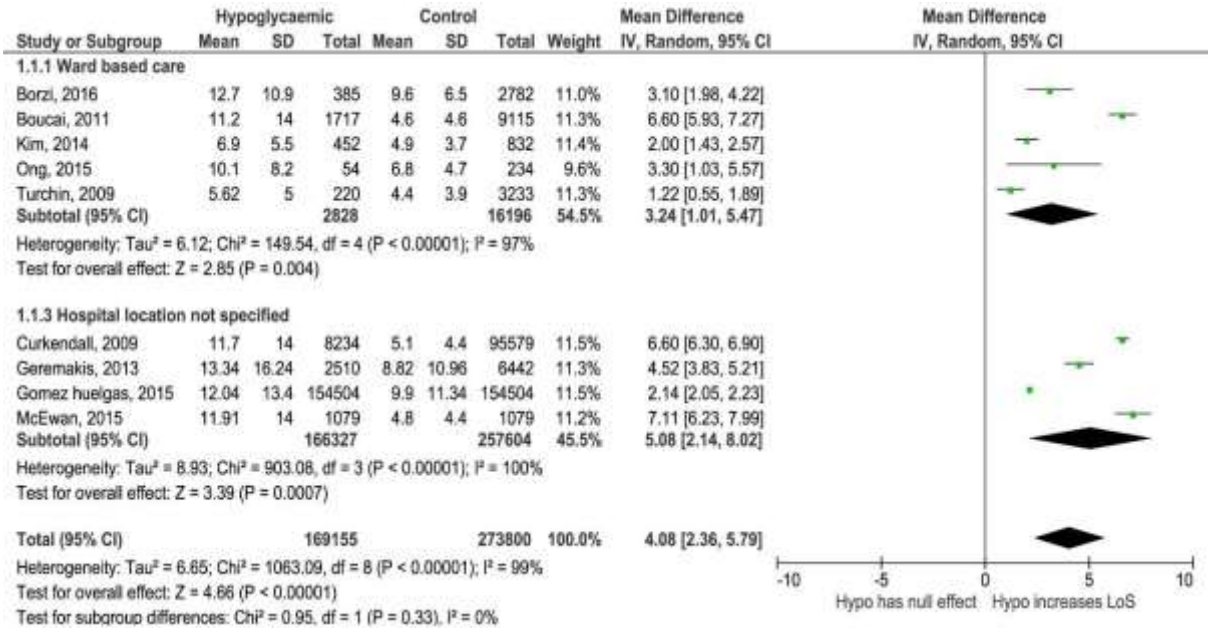
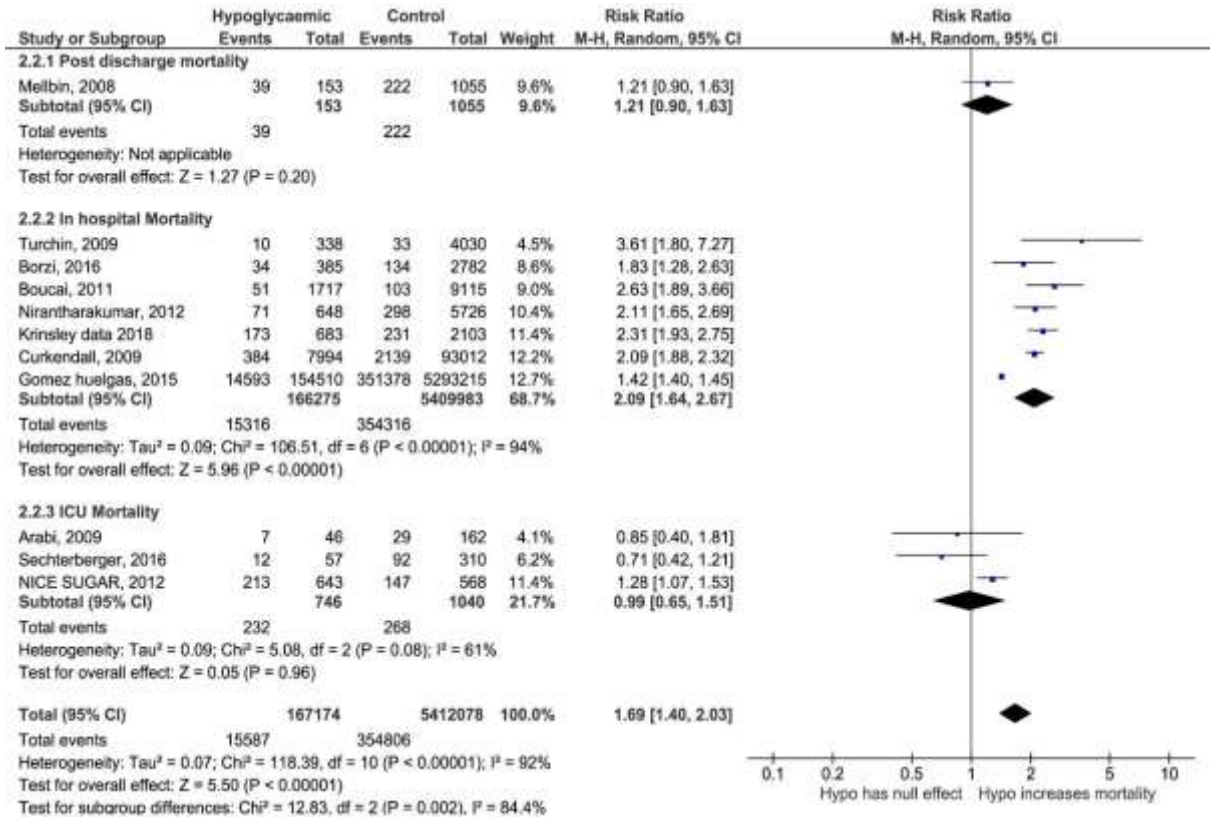


Figure 2b – Inpatient hypoglycaemia and mortality forest plot



Appendix:

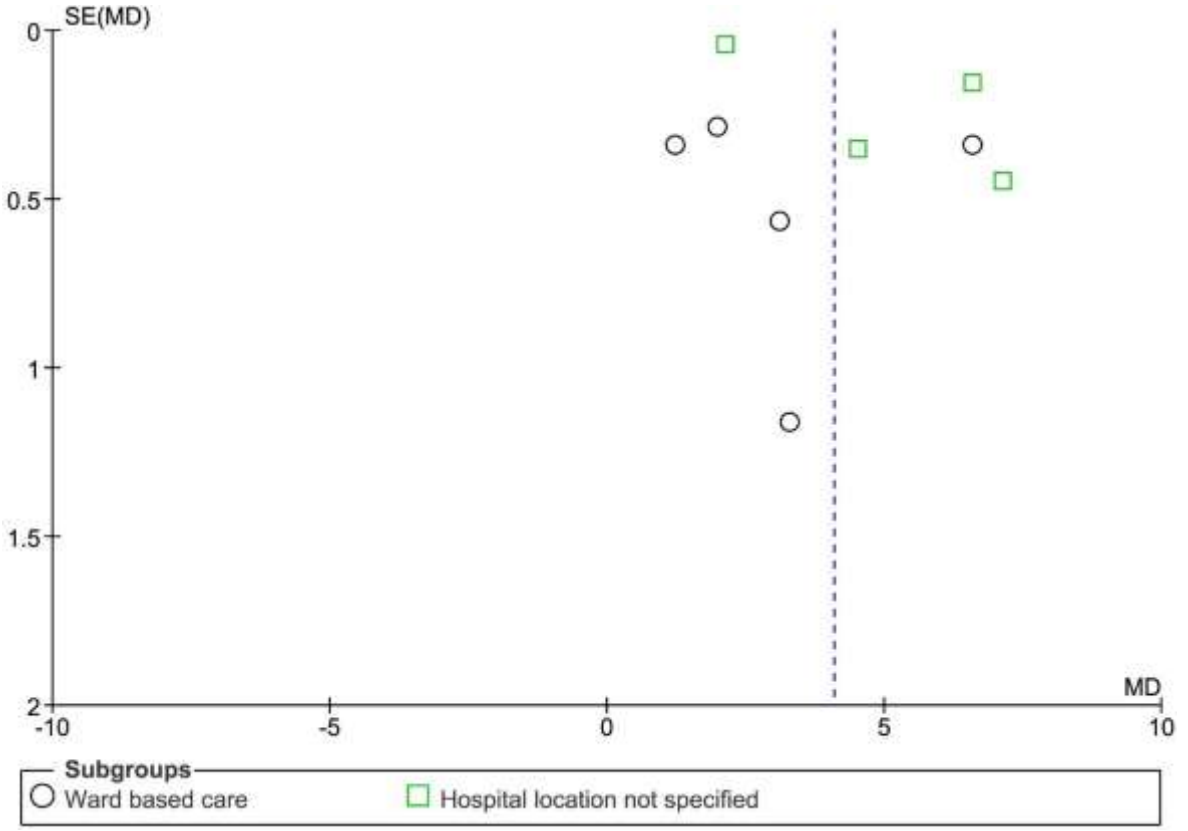
Appendix 1 - Final search strategy used in MEDLINE

Ovid MEDLINE (R) 1946 to June Week 3 2017

1. Diabetes Mellitus.mp. or exp Diabetes Mellitus/
2. diab*.mp.
3. 1 or 2
4. exp Hospitalization/
5. hospitali*.mp.
6. 4 or 5
7. Hypoglycemia/ or hypoglycemia.mp.
8. Hypoglycaemia.mp.
9. (low adj2 glucose).mp.
10. (low adj2 sugar).mp.
11. 7 or 8 or 9 or 10
12. 3 and 6 and 11
13. Limit 12 to English language

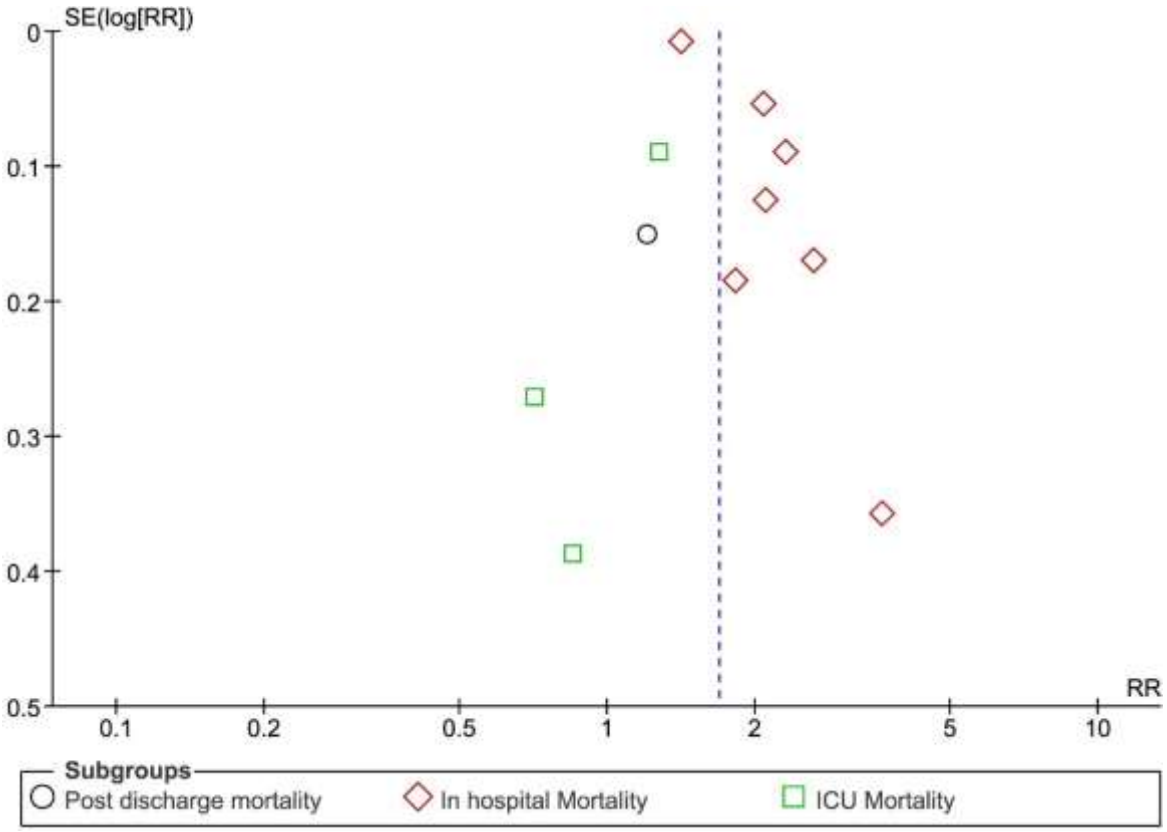
Appendix 2 – Small study effect; Figure 1a

1a Hypoglycaemia and length of stay funnel plot



Appendix 2 – Small study effect; Figure 1b

1b Hypoglycaemia and mortality funnel plot



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Cover Page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Apendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2a & 2b
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A - Student

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097