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## RESEARCH: CARE DELIVERY

# The effects of a leaflet-based intervention, ‘Hypos can strike twice’, on recurrent hypoglycaemic attendances by ambulance services: A non-randomised stepped wedge study

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## Abstract

**Aims:** We aimed to investigate the effect of an intervention in which ambulance personnel provided advice supported by a booklet—‘Hypos can strike twice’—issued following a hypoglycaemic event to prevent future ambulance attendances.

**Methods:** We used a non-randomised stepped wedge-controlled design. The intervention was introduced at different times (steps) in different areas (clusters) of operation within East Midlands Ambulance Service NHS Trust (EMAS). During the first step (T0), no clusters were exposed to the intervention, and during the last step (T3), all clusters were exposed. Data were analysed using a general linear mixed model (GLMM) and an interrupted-time series analysis (ITSA).

**Results:** The study included 4825 patients (mean age 65.42 years, SD 19.42; 2,166 females) experiencing hypoglycaemic events attended by EMAS. GLMM indicated a reduction in the number of unsuccessful attendances (i.e., attendance followed by a repeat attendance) in the final step of the intervention when compared to the first (odds ratio OR: 0.50, 95%CI: 0.33–0.76,  $p = 0.001$ ). ITSA indicated a significant decrease in repeat ambulance attendances for hypoglycaemia—relative to the pre-intervention trend ( $p = 0.008$ ). Furthermore, the hypoglycaemia care bundle was delivered in 66% of attendances during the intervention period, demonstrating a significant level of practice change ( $p < 0.001$ ).

**Conclusion:** The ‘Hypos can strike twice’ intervention had a positive effect on reducing numbers of repeat attendances for hypoglycaemia and in achieving the care bundle. The study supports the use of information booklets by ambulance clinicians to prevent future attendances for recurrent hypoglycaemic events.

## KEYWORDS

hypoglycaemia, leaflet-based intervention, stepped-wedge design

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# 1 | INTRODUCTION

## 1.1 | Background

Hypoglycaemia is a condition characterised by lower than normal levels of blood glucose leading to sympathoadrenal (e.g., sweating, palpitations and dizziness) and neuroglycopenic (e.g., confusion, drowsiness and loss of consciousness) effects.<sup>1</sup> It is a serious acute complication of diabetes therapy, requiring prompt recognition and treatment.<sup>2</sup>

Hypoglycaemia is often treated by patients themselves, family members or those caring for them, but severe hypoglycaemia, defined as severe symptoms requiring external assistance for recovery, often requires ambulance attendance which may result in hospital admission.<sup>3</sup>

Severe hypoglycaemia constitutes around 0.6% of the emergency calls attended by the East Midlands Ambulance Service NHS Trust (EMAS) and its annual costs are estimated to be £235,407.<sup>4</sup> Moreover, the estimated cost of managing insulin-related hypoglycaemia in the UK is £468.0 million, £295.9 million for severe episodes and £172.1 million for non-severe episodes.<sup>5</sup> Hypoglycaemia can have serious repercussions on patients' health such as brain damage<sup>2</sup> or increased risk of cardiovascular disease.<sup>6</sup> It also adds medical costs, burdening health services.<sup>7–9</sup> Furthermore, hypoglycaemia can have a negative psychological impact on both patients and their relatives, impairing quality of life and worsening long-term diabetes control.<sup>10,11</sup>

Impaired awareness, where signs of hypoglycaemia are not recognised, is a common feature of ambulance calls for this condition.<sup>12</sup> Reduced awareness affects around 25% of adults with type 1 and 10% of those with type 2 diabetes with hypoglycaemia and dramatically increases the chances of a subsequent event.<sup>13,14</sup> Notably, patients attended by ambulance services are predisposed to having recurrent events and require changes in therapy or lifestyle advice (on diet or exercise) to prevent further events.<sup>15</sup> Post-hypoglycaemic patients treated in the prehospital environment have a 2%–7% risk of experiencing a repeat hypoglycaemic event within 48 h and up to 18% within 3 months.<sup>16</sup>

A previous systematic review and meta-analysis underlined the importance of educating and informing diabetes patients about their condition and the risks associated with it, since knowledge about their condition can play an important role in maintaining glycaemic control and preventing further complications and events.<sup>17</sup> Kumaran et al.<sup>18</sup> provide further evidence that patients with diabetes could be helped by providing them with educational leaflets which explain how to better manage their condition. Another systematic review concluded that information leaflets (booklets) can improve patients' knowledge and satisfaction.<sup>19</sup> Sankar et al.<sup>20</sup> identified positive outcomes from the use of leaflets with patients suffering from diabetes, translated into adherence

### What's new

- Patient education is important for maintaining glycaemic control and preventing recurrent hypoglycaemia; however, evidence is mixed.
- The 'Hypos can strike twice' intervention showed that information booklets can have a positive effect on reducing numbers of repeat ambulance attendances for hypoglycaemic episodes; moreover, it benefitted from a large sample of 4825 patients attended by ambulance services over a period of over 2 years, showing the importance of patient education when managing hypoglycaemia.
- The study supports the use of information booklets by ambulance clinicians to prevent future attendances and reduce health costs for recurrent hypoglycaemic events.

to treatment with fewer recurrent hypoglycaemic events and hospital admissions. However, some evidence has also indicated that the leaflets may not have the expected results, especially in elderly patients who encounter difficulties in understanding the content of the leaflets unless they are very well designed.<sup>21</sup>

In conclusion, there is a consensus that informing and educating diabetes patients about their condition can have a positive impact on their health, but the evidence regarding the efficacy of ambulance staff providing advice supported by information leaflets is neither comprehensive nor conclusive. The present study addresses this gap and further investigates the role of information leaflets in the recovery and prevention of recurrent hypoglycaemic events.

## 1.2 | Aims of this investigation

The primary objective of the study was to assess the effect of introducing the *Hypos can strike twice* intervention. The intervention consisted of ambulance clinicians providing advice and a booklet to patients to prevent a recurrent ambulance attendance. Patients were given the booklet for them to read when fully recovered from the hypoglycaemic event. The booklet can be seen in the Supporting Information, Section D. The main expectation was that patients' behaviour would change following the booklet advice so that a second hypoglycaemic episode would be prevented. As such, the main hypothesis was that the intervention would prevent recurrent ambulance attendances for another hypoglycaemic episode.

A second expectation was that the treatment process would become more structured given the fact that the

booklet encouraged ambulance staff to fill in a treatment section. As such, a secondary objective was to assess if a care bundle for hypoglycaemia (i.e., treatment recorded and blood glucose recorded before and after treatment for hypoglycaemia) was achieved and if this was influenced by the intervention.

## 2 | MATERIALS AND METHODS

### 2.1 | Ethics

Ethical approval was obtained from the NHS Research Ethics Committee (IRAS project ID: 276438 REC reference: 20/YH/0082) and Research and Development approval from EMAS. The data are from human subjects, but we did not obtain informed consent because the design involved use of routine anonymised data.

### 2.2 | Study design and setting

A non-randomised stepped-wedge design was used for evaluating the effectiveness of the intervention.<sup>21</sup> The methods and results are reported following the Hemming et al.<sup>22,23</sup> guidelines. This design was chosen because it accounted for differences between clusters, it allowed *all* clusters to be exposed to both control and intervention periods, and it accommodated the logistical problems posed by the readiness of each area to implement the intervention. The design consisted of an intervention period, when the advice and information booklet *Hypos can strike twice* was given to patients seen by ambulance staff for severe hypoglycaemia, and a non-intervention period, before the booklet was provided. The design allowed all areas of a regional ambulance service (clusters) to be exposed to the intervention, overcoming ethical issues raised by choosing only certain areas that would benefit from the intervention. The areas (or clusters) were Leicestershire and Northamptonshire (L&N), Derbyshire and Nottinghamshire (D&N), and Lincolnshire (L). An initial control period during which no

cluster was exposed to the intervention was followed by time intervals ('steps') when each cluster crossed from the control to the intervention. Data were provided by EMAS for 26 months from September 2017 to November 2019, during which all clusters were exposed to control and intervention periods (Table 1).

### 2.3 | Data collection and pre-processing

Routine anonymised data in which individual patients were assigned a unique (non-personally identifiable) number were collected from EMAS 13 months before the intervention was first introduced and 11 months following this time point.

The data included call categories, date and time, geographical location, demographics (age, sex and ethnicity), clinical information (chief complaint and impression group), physiological measurements taken (including blood glucose levels) and treatments given.

Patients were selected based on the clinical information provided, blood glucose levels and location. First, only patients who had been attended for severe hypoglycaemia (i.e., attended by a third party—ambulance services—with blood glucose levels under 4 mmol/L) were included in the analyses. Patients were also assigned to one of the clusters based on their geographical location of the attendance indicated by the post code.

The main outcome variable was binary and coded as a 0 ('success') or 1 ('fail'). The outcome was considered a success if the first attendance to the patient was *not* followed by a second attendance for the duration of the study. Analogously, the outcome was considered unsuccessful (a fail) if the first attendance was followed by a second.

### 2.4 | Statistical analyses

The first model, a general linear mixed model (GLMM), was fitted to the data, with clusters specified as random effects and time periods (T0, T1, T2 and T3) and intervention

**TABLE 1** Schematic representation of stepped-wedge study design showing clusters with control and intervention periods

Cluster	Time (Steps)			
	T0 03/09/2017–30/11/2018 (13 months)	T1 01/12/2018–28/02/2019 (3 months)	T2 01/03/2019–31/05/2019 (3 months)	T3 01/06/2019–01/11/2019 (5 months)
1st Cluster L&N	0	1	1	1
2nd Cluster N&D	0	0	1	1
3rd Cluster L	0	0	0	1

Note: 0, no intervention; 1, intervention.

periods (intervention and no-intervention) as fixed effects. The model used was the time-adjusted model proposed by Hussey and Hughes<sup>23</sup> which allowed the fitting of both intervention and time to the data. Following an intention-to-treat principle, clusters were analysed according to their crossover time irrespective of whether the crossover had been achieved at the desired time. Seasonality (i.e., month of the year), patient age (divided into age groups of 10 years ranging from under 30 years old to over 90 years old), gender (divided into three categories: female—used as baseline, male and transgender) and deprivation deciles (values ranged from 1 to 10, 1 corresponding to the highest deprivation level and 10 to the lowest) were included as covariates in the model. Missing values were not included in the model which was run on a sample of 4799 observations. The analysis was run in Stata15.1 (©StataCorp LLC) using the *melogit* function for binary outcome.

A second model, an interrupted time series analysis (ITSA), was fitted to the data.<sup>24</sup> The main outcome variable (i.e., how successful a call was) was averaged per each week before and after the intervention was introduced. This model allowed a more robust analysis which consisted in the alignment of all clusters at the time the intervention started (T0), thus simultaneously including the observations from all clusters grouped within individual weeks from pre- or post-intervention time. Seasonality (i.e., month of the year), patient age (divided in age groups of 10 years), gender and deprivation were averaged per week and included as covariates in the model. The analysis was run in Stata15.1 (©StataCorp LLC) using the *itsa* function.<sup>25</sup>

A third descriptive analysis was run to establish if the care bundle had been achieved; more specifically, the number of times a treatment (i.e. a drug for hypoglycaemia) was given prior and after the blood glucose measurement was taken.

A significance level of 5% was used throughout with no allowance of multiplicity of the statistical tests.

## 3 | RESULTS

### 3.1 | Patients

All patients who were attended for a hypoglycaemic event (i.e., blood glucose levels recorded were lower than 4 mmol/L) in the time period extending from September 2017 to November 2019 were included in the study. A total of 4825 patients were included in the study. Their age ranged from 16 to 104 years old ( $M = 65.42$ ,  $SD = 19.42$ ). There were 2166 (45.10%) females, 2633 (54.82%) males and 4 (0.08%) transgender patients (22 patients lacked gender data). The patients seen in the pre- and post-intervention period did not differ by age ( $p = 0.189$ ) or gender ( $p = 0.181$ ).

## 3.2 | Results: Primary objective

### 3.2.1 | GLMM results

A GLMM was fitted to the data examining the number of repeat attendances shown for each cluster in Table 2.

The model adjusted for covariates of deprivation, age, gender and seasonality (i.e., month of the year). The baseline was represented by no intervention and control period (T0). When comparing the time periods or steps corresponding to when the intervention was introduced for each cluster, there was a decreased likelihood of a repeat attendance in T3 compared to T0 (OR: 0.50 [95% CI 0.33, 0.76],  $p = 0.001$ ). Deprivation was a significant predictor, lower deprivation levels associated with a reduced likelihood of a repeat attendance (OR: 0.94 [95% CI 0.91, 0.97],  $p = 0.001$ ). Gender was also a significant predictor, males being more likely to have a repeat attendance (OR: 1.19 [95% CI 1.02, 1.38],  $p = 0.023$ ). Intra-cluster correlation was low for all outcomes (i.e., close to zero) indicating that the within-cluster variance was higher than between-cluster variance. A detailed account of these results can be seen in Table 3.

### 3.2.2 | ITSA results

An ITSA was also fitted to the data, allowing for alignment of all clusters to T0, the time the intervention started whilst considering secular trends before the intervention started.

The main outcome variable was represented by the mean (proportion) of incidents followed by a repeat attendance (unsuccessful episodes) per week. After inspecting the box plot of the outcome variable, one outlier was identified with a value of 1, and this observation was excluded. Normality was checked using both histograms and Q-Q plots. The histogram indicated a normal distribution with most values falling between 0.2 and 0.3. The Q-Q plot also indicated a normal distribution; both the proportion of unsuccessful calls and residuals did not strongly deviate from the line (the plots can be seen in the Supporting Information, Section C, in Figures S.C1, S.C2 and S.C3). Shapiro-Wilk and Skewness/Kurtosis tests for normality were non-significant ( $p = 0.14$  and  $p = 0.19$ , respectively), indicating that the assumption of normality was not violated (see Table S.C4). The autocorrelations graphs indicated no spikes with values significantly different from '0', providing evidence against autocorrelation and suggesting a lag of 0 (the graphs can be seen in the Supporting Information, Section C, Figure S.C4).

After aligning all clusters, the starting level of mean attendances followed by a repeat attendance per week was estimated at 0.04 (SE: 0.25, CI:  $-0.44/0.53$ ) and decreased before the start of the intervention at a rate of 0.0002 (SE: 0.0003, CI:  $-0.0009/0.0005$ ). In the first day of the intervention, the

**TABLE 2** Number (and percentage) of episodes with or without repeat attendances for each cluster before and after the start of the intervention

	Cluster 1		Cluster 2		Cluster 3	
	Intervention		Intervention		Intervention	
	No	Yes	No	Yes	No	Yes
Successful episodes, i.e., without repeat attendance	687 (80.07%)	665 (84.82%)	1043 (80.67%)	616 (86.15%)	689 (76.81%)	241 (86.69%)
Unsuccessful episodes, i.e., with a repeat attendance	171 (19.93%)	119 (15.18%)	250 (19.33%)	99 (13.85%)	208 (23.19%)	37 (13.31%)

predicted level of the post-intervention trend was lowered by 0.034 (SE: 0.025, CI: -0.083, 0.015). It was followed by a decrease of 0.003 (SE: 0.001, CI: -0.004, -0.0007) of unsuccessful episodes relative to the pre-intervention trend, which was significant ( $p = 0.008$ ). After the start of the intervention, the overall decrease was of 0.003 (SE: 0.0009, CI: -0.0045/-0.0010), and this was significant too ( $p = 0.003$ ).

**TABLE 3** GLMM results showing the effect of the intervention and of covariates

	Odds ratio	95% confidence interval	<i>p</i> value
Intervention	1.04	0.74, 1.48	0.797
T1	1.06	0.82, 1.36	0.671
T2	0.74	0.52, 1.06	0.103
T3	0.50	0.33, 0.76	0.001
Deprivation	0.94	0.91, 0.97	0.001
Month	1.01	0.99, 1.03	0.307
Age	0.97	0.93, 1.01	0.078
Gender	1.19	1.02, 1.38	0.023
ICC	0.006 (95% CI: 0.000, 0.116)		

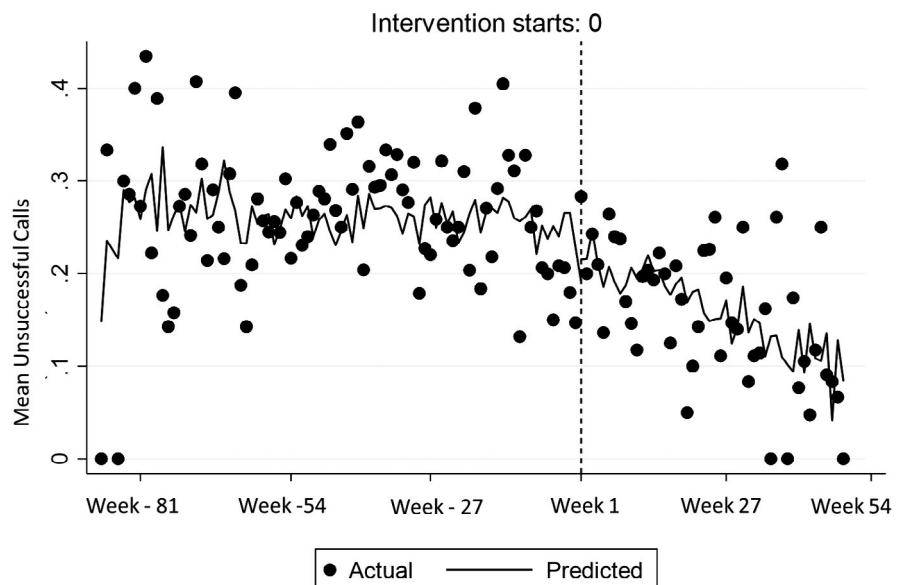
Abbreviation: GLMM, general linear mixed model.

None of the co-variates reached a significant level set at  $\alpha = 0.05$ . The results can be seen in Figure 1.

### 3.3 | Results: Secondary objective

#### 3.3.1 | Care bundle

Four main types of treatment were administered by ambulance clinicians for hypoglycaemia. These included glucose, glucagon, GlucoGel and oral carbohydrates. Overall, 68% of patients seen by ambulance staff, representing a total number of 3281 patients, received at least one type of drug. The most popular treatment used was GlucoGel, given in 37.1% of cases, followed by glucagon (24.3%), glucose (23.7%) and oral carbohydrates (3.3%); the remaining 11.6% represented other types of drugs which were not for hypoglycaemia (e.g., paracetamol, co-codamol, aspirin and sodium chloride). Recordings of vital signs included heart rate, blood pressure, blood glucose, respiratory rate, oxygen saturation, temperature and Glasgow coma scale. Blood glucose and heart rate measurements were taken once for all patients (100% of cases).



**FIGURE 1** Interrupted-time series analysis results for aligned clusters

Regarding the care bundle (measurement-treatment-measurement), blood glucose measurements were taken at least twice in 95.9% of cases (i.e., for 4,628 patients). This was accompanied by the administration of treatment in 66.2% of cases (i.e., for 3,193 patients). More detailed results are presented in Table 4.

The care bundle was achieved more often during the intervention period compared to the non-intervention period ( $p < 0.001$ ). This occurred in cluster 1 ( $p = 0.003$ ) and cluster 2 ( $p < 0.001$ ), but not in cluster 3 ( $p = 0.653$ ).

## 4 | DISCUSSION

### 4.1 | Main findings

The study shows that a pragmatic intervention of *Hypocan strike twice* administered by ambulance staff resulted in a significant prevention of recurrent call-outs for hypoglycaemia, and therefore a positive effect of the intervention on recurrent hypoglycaemic events requiring ambulance attendance, using a non-randomised stepped-wedge study design comprising four steps and three clusters. The study indicated a positive effect of the intervention when looking at the overall outcome of unsuccessful episodes. More precisely, the GLMM analysis indicated that this number statistically significantly decreased in the last step of the intervention (T3), when all clusters were exposed to the intervention, compared to the first step of the intervention (T0), the control period when none of the clusters were exposed. However, the results of the GLMM analysis indicated the opposite trend when looking at unsuccessful calls (i.e., calls followed by a repeat) within certain time periods, but these results were strongly influenced by the exclusion of a considerable number of calls from the last two steps (T2 and T3) of the intervention (results are shown in the Supporting Information, Section A, Table S.A1).

The ITSA analysis indicated a clear trend of a decreasing number of 'unsuccessful' incidents in the post-intervention period. This approach seemed to be more robust because it accounted for the secular trends prior to the intervention

period and it also allowed the alignment of all clusters at the time the intervention started, directly comparing all calls prior to the intervention and post intervention.<sup>25,26</sup> Thus, the results of ITSA indicated a reduced number of unsuccessful calls in the post-intervention period when aligning all clusters which was maintained for clusters two and three (details are presented in the Supporting Information, Section B). Moreover, the time to a repeat attendance was longer in the intervention period when compared to the non-intervention period (see the Supporting Information, Section E, Figure S.E1).

### 4.2 | Comparison with previous literature

Previous evidence has suggested that education plays an important role in maintaining glucose control and preventing hypoglycaemic events.<sup>17</sup> However, the means of reaching this target can vary from structured educational programmes including education on diabetes<sup>27</sup> and on related conditions such as stress-management,<sup>28</sup> to offering information leaflets or providing constant technological monitoring of glucose levels.<sup>29</sup> Sankar et al.<sup>20</sup> showed improvement in knowledge and glycaemic control in patients following a leaflet-based intervention. Importantly, intervention was more beneficial in more educated patients. Kim et al.<sup>21</sup> suggested that leaflets are more efficient when patients better understand their content, and this aspect is influenced by patients' older age. Our study found a significant influence of deprivation on the outcome, which is also associated with lower levels of education, patients from more deprived areas being more likely to have recurrent incidents. There was also a significant effect of gender, with male patients being more likely to have a recurrent hypoglycaemic event. A series of biological, psychological and sociocultural factors predispose people to diabetes and influence its development, but certain factors such as drinking alcohol or sleep deprivation are most likely to influence higher incidence in men than women.<sup>30</sup> Age did not significantly predict the outcome, but there was a trend towards lower likelihood of a hypoglycaemic event in elderly patients.

	Care bundle			
	Achieved		Not achieved	
	Intervention (%)	No intervention (%)	Intervention (%)	No intervention (%)
All clusters	71.1	63.3	28.9	36.7
Cluster 1	70.2	63.2	29.9	39.8
Cluster 2	73.7	62.0	26.3	38.1
Cluster 3	66.9	65.4	33.1	34.6

**TABLE 4** Care bundle achieved or not comparing intervention and non-intervention periods

Whilst previous research identifies a positive value in the use of informative leaflets,<sup>17</sup> most studies recognise the importance of an eclectic approach towards hypoglycaemia management which would include informative programmes (e.g., leaflets), but also close monitoring, controlled drug treatment and frequent contact with a specialised hypoglycaemia service.<sup>31</sup> Regarding this aspect, our study acknowledges the importance of monitoring and additional care services such as referrals to an appropriate healthcare professional, but the data received did not include this information; thus, it was not possible for us to further investigate it.

### 4.3 | Strengths and limitations

The key strength of this study is the simple pragmatic intervention. The present study also benefitted from a large sample (4,825 patients) and a high proportion (884 [18.34%]) of recurrent hypoglycaemic incidents over 26 months. Moreover, the non-randomised stepped-wedge study design allowed all clusters to be exposed to the intervention, overcoming ethical considerations of no intervention or randomisation.<sup>21</sup>

The study was conducted following an intention-to-treat principle, clusters being analysed according to their cross-over time with no guarantee that the intervention had taken place. Furthermore, diabetes patients were assigned to their clusters by postcodes, regardless of the location of their clinical facility. Thus, keeping a better record of the leaflet and of the overall treatment provided to the patient would offer more comprehensive findings. Other limitations include the lack of data on the type of diabetes (i.e., type 1 or type 2) and on patient reported outcomes. These data are routinely collected and not purposefully collected for research. As such, the researchers cannot decide which measurements should be taken; they only process the data received from ambulance services in its standard format.

### 4.4 | Implications

The present study supports the practice of ambulance clinicians, not only responding appropriately to an urgent call for a patient with hypoglycaemia but also informing and educating diabetes patients about the recurrent risks of hypoglycaemia to prevent future episodes through direct advice supported by an information leaflet.

National UK ambulance bodies such as the Association of Ambulance Chief Executives (AACE) and National Ambulance Services Medical Directors' Group (NASMed) have recommended the introduction of community pathways for people with diabetes and hypoglycaemia, but these need to be evaluated further. This NHS 10 year plan has a focus on delivering 'world-class care for people with major health

problems' such as diabetes, by 'helping more people to live independently at home for longer' and 'developing more rapid community response teams to prevent unnecessary hospital spells, and speed up discharges home'.

The study showed that a low-cost pragmatic leaflet-based intervention was effective in reducing callouts for recurrent hypoglycaemia. The intervention can be of great value for ambulance services, especially due to its low cost, the cost being estimated at only £3.70 per administration of which £3.60 are due to extra staff time and £0.10 to the production of the leaflet. The simplicity of the intervention means it could easily be scaled up to other services, but effects were small, suggesting that behavioural theory-informed complex interventions which include direct referrals to community pathways should be tested and evaluated further.

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### CONFLICT OF INTEREST

The authors have no commercial, financial and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see [www.icmje.org](http://www.icmje.org)). The study was funded by NIHR Applied Research Collaboration, but study design and analysis were carried out independently of the funder who had no role in the conduct or analysis of the research or preparation of the manuscript.

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### REFERENCES

1. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in type 2 diabetes. *Diabet Med*. 2008;25(3):245-254.
2. Warren RE, Frier BM. Hypoglycaemia and cognitive function. *Diabetes Obes Metab*. 2005;7(5):493-503.
3. Heller SR, Frier BM, Hersløv ML, et al. Severe hypoglycaemia in adults with insulin-treated diabetes: impact on healthcare resources. *Diabet Med*. 2016;33(4):471-477.
4. Khunti K, Fisher H, Paul S, et al. Severe hypoglycaemia requiring emergency medical assistance by ambulance services in the East Midlands: a retrospective study. *Prim Care Diabetes*. 2013;7(2):159-165.



5. Parekh WA, Ashley D, Chubb B, Gillies H, Evans M. Approach to assessing the economic impact of insulin-related hypoglycaemia using the novel local impact of hypoglycaemia tool. *Diabet Med*. 2015;32(9):1156-1166.
6. Fährmann ER, Adkins L, Loader CJ, et al. Severe hypoglycemia and coronary artery calcification during the diabetes control and complications trial/epidemiology of diabetes interventions and complications (DCCT/EDIC) study. *Diabetes Res Clin Pract*. 2015;107(2):280-289.
7. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ*. 2011;343:d6898.
8. Goto A, Arah OA, Goto M, et al. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ*. 2013;347:f4533.
9. Yeh JS, Sung S-H, Huang H-M, et al. Hypoglycemia and risk of vascular events and mortality: a systematic review and meta-analysis. *Acta Diabetol*. 2016;53(3):377-392.
10. Currie CJ, Morgan CL, Poole CD, et al. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. *Curr Med Res Opin*. 2006;22(8):1523-1534.
11. Davis RE, Morrissey M, Peters JR, et al. Impact of hypoglycaemia on quality of life and productivity in type 1 and type 2 diabetes. *Curr Med Res Opin*. 2005;21(9):1477-1483.
12. Geddes J, Schopman JE, Zammitt NN, et al. Prevalence of impaired awareness of hypoglycaemia in adults with Type 1 diabetes. *Diabet Med*. 2008;25(4):501-504.
13. Schopman JE, Geddes J, Frier BM. Frequency of symptomatic and asymptomatic hypoglycaemia in Type 1 diabetes: effect of impaired awareness of hypoglycaemia. *Diabet Med*. 2011;28(3):352-355.
14. van Meijel LA, de Vegt F, Abbink EJ, et al. High prevalence of impaired awareness of hypoglycemia and severe hypoglycemia among people with insulin-treated type 2 diabetes: The Dutch Diabetes Pearl Cohort. *BMJ Open Diabetes Res Care*. 2020;8(1):e000935.
15. De Galan BE, Schouwenberg BJ, Tack CJ, Smits P. Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. *Neth J Med*. 2006;64(8):269-279.
16. Fitzpatrick D, Duncan EA. Improving post-hypoglycaemic patient safety in the prehospital environment: a systematic review. *Emerg Med J*. 2009;26(7):472-478.
17. Yeoh E, Choudhary P, Nwokolo M, Ayis S, Amiel SA. Interventions that restore awareness of hypoglycemia in adults with type 1 diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2015;38(8):1592-1609.
18. Kumaran KSGA, Palanisamy S, Rajasekaran A. Development and implementation of patient information leaflets in diabetes mellitus. *J Pharm Health Serv Res*. 2010;1:85-89. <https://doi.org/10.1111/j.1759-8893>
19. Sustersic M, Gauchet A, Foote A, et al. How best to use and evaluate Patient Information Leaflets given during a consultation: a systematic review of literature reviews. *Health Expect*. 2017;20(4):531-542.
20. Sankar V, Sherif A, Sunny AA, John GM, Rajasekaran SK. The impact of patient information leaflets to prevent hypoglycemia in out-patients with type 2 diabetes mellitus. *Ars pharm*. 2019;60(1):5-14.
21. Kim J, Shim H, Lee IH. Developing and evaluating a drug information leaflet of antidiabetics for senior citizens; employing performance-based user-testing. *Korean J Clin Pharm*. 2017;27(3):171-177.
22. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ*. 2015;6(350):h391.
23. Hemming K, Taljaard M, McKenzie JE, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. *BMJ*. 2018;363:k1614.
24. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials*. 2007;28(2):182-191.
25. Linden A. Conducting interrupted time-series analysis for single- and multiple-group comparisons. *Stata J*. 2015;15(2):480-500.
26. McDowall D, McCleary R, Bartos BJ. *Interrupted time series analysis*. Oxford University Press; 2019.
27. Cox DJ, Gonder-Frederick L, Julian D, et al. Intensive versus standard blood glucose awareness training (BGAT) with insulin-dependent diabetes: mechanisms and ancillary effects. *Psychosom Med*. 1991;53(4):453-462.
28. Cox DJ, Gonder-Frederick L, Julian DM, Clarke W. Long-term follow-up evaluation of blood glucose awareness training. *Diabetes Care*. 1994;17(1):1-5.
29. Ryan EA, Germsheid J. Use of continuous glucose monitoring system in the management of severe hypoglycemia. *Diabetes Technol Ther*. 2009;11(10):635-639.
30. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocr Rev*. 2016;37(3):278-316.
31. Choudhary P, Rickels MR, Senior PA, et al. Evidence-informed clinical practice recommendations for treatment of type 1 diabetes complicated by problematic hypoglycemia. *Diabetes Care*. 2015;38(6):1016-1029.

## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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