**Ethnic variations in the risk of hypoglycaemia among people with type 2 diabetes prescribed insulins and/or sulphonylureas: a historical cohort study using general practice-recorded data.**

*Short Title*

*Type 2 Diabetes: Ethnicity and hypoglycaemia in primary care*

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Manuscript and abstract word count: 3,217

Conflicts of interest: None

Novelty statement:

* This study explored ethnic group differences in the risk of hypoglycaemia among people with type 2 diabetes prescribed insulins and/or sulphonylureas using primary-care recorded data with near-complete ethnicity recording.
* Those individuals of Black Caribbean ethnicity prescribed either insulins and/or sulphonylureas, as well as Black Africans and Indians prescribed sulphonylureas were at increased hypoglycaemic risk compared to White British groups. Bangladeshis prescribed insulins were at lower risk of hypoglycaemia than other South Asian groups.
* Such differences in hypoglycaemic risk warrant further investigation to determine the appropriateness of universal treatment targets across all ethnicities.

# Acknowledgements

This study was supported by Queen Mary University of London. It is dependent upon the goodwill of patients to share their de-personalised data and the work of the general practitioners and their staff across the three Clinical Commissioning Groups (Tower Hamlets, Newham and City & Hackney) who were responsible for entering high quality data on the study participants and giving their consent to the research uses of these data for patient benefit. The Clinical Effectiveness Group, Queen Mary University of London, provided support for the web-enabled data extraction.

Abstract

## Aim

To identify ethnic differences in hypoglycaemic risk among people with type 2 diabetes prescribed insulins and/or sulphonylureas in community settings.

## Methods

Using routine GP-recorded data, two cohorts of adults with type 2 diabetes from east London were studied between January 2013 and December 2015: those prescribed (1) insulins +/- other anti-diabetes medications (n=7,269); or (2) sulphonylureas +/- other anti-diabetes medications excluding insulins (n=12,502). Incidence rate ratios (IRR) of hypoglycaemia by ethnicity, adjusting for age, sex, socioeconomic status and clustering within Clinical Commissioning Groups, were estimated using random effects Poisson regression.

## Results

Compared to White British participants prescribed insulins, those of Black Caribbean ethnicity were at increased hypoglycaemic risk: adjusted IRR 1.56 (95% CI, 1.21,2.01); while Bangladeshis had lower risk, adjusted IRR 0.49 (95% CI, 0.38,0.64). In the sulphonylurea cohort, Black Caribbeans, Black Africans and Indians all had increased risks of hypoglycaemia compared to White British participants: adjusted IRR 1.63 (95% CI, 1.15,2.29), 1.90 (95% CI, 1.32,2.75) and 1.93 (95% CI, 1.39,2.69) respectively.

## Conclusion

The differences in hypoglycaemic risk among people with type 2 diabetes prescribed insulin and/or sulphonylureas warrant further investigation of any differing biological responses and/or cultural attitudes to anti-diabetes therapy between ethnic groups and should be considered by clinicians evaluating the treatment goals of their patients with type 2 diabetes using insulins or sulphonylureas.

# Introduction

Intensive glycaemic control using insulins and sulphonylureas substantially increases the risk of hypoglycaemia.(1–3) Most hypoglycaemia is asymptomatic and self-managed but when more severe is characterised by autonomic and neuroglycopenic symptoms, which may be fatal if not treated promptly and is associated with increasing hospital admissions.

## Ethnicity and hypoglycaemia

A recent study of hypoglycaemia in hospital settings in the UK found that Black Caribbean people were at higher risk of hospitalisation due to hypoglycaemia than White Europeans but Bangladeshis, Pakistanis and Indians were at lower risk.(4) There is also limited evidence, mainly from hospital settings in the United States, that ethnic minority groups (African-Americans, Hispanics and Asians) with type 2 diabetes are at increased risk of hypoglycaemia compared to non-Hispanic Whites.(5–8)

The effects of therapy may vary according to an individual’s ethnicity. For example, African Americans in a large health system had better glycaemic responses to metformin than their European American counterparts.(9) Furthermore, analysis of eleven multinational trials found that those of African and Asian descent using insulins had significantly higher risks of hypoglycaemia compared to White Europeans.(10) Additionally, South Asians appear less compliant with insulin regimes or prefer the use of simpler basal only insulins.(11–13)

The aim of this research was to establish whether the risk of clinically-recorded hypoglycaemia in primary care records differ between and within the major ethnic groups in east London after adjusting for age, sex, socioeconomic deprivation and clustering within Clinical Commissioning Groups (CCG) in those with type 2 diabetes prescribed insulins and/or sulphonylureas. Given possible ethnic variations in adherence and responses to anti-diabetes agents, a secondary aim was to identify any interaction between ethnicity and type of anti-diabetes medication, i.e. insulins or sulphonylureas, on the risk of hypoglycaemia. This is the first UK study designed to examine the relationship of hypoglycaemia and ethnicity in a diverse ethnic population with type 2 diabetes already prescribed intensive oral treatments and/or insulins using routine GP-recorded primary care data, which includes socioeconomic status.

# Materials and methods

## Study Design

An observational cohort study was performed using routinely collected primary care data from the electronic health records (EHR) of patients from all 128 general practices in the east London CCGs of Tower Hamlets, Newham, and Hackney (including the City of London) between 1st January 2013 and 31st December 2015. We securely extracted non-identifiable patient data from the EHR of patients registered with participating practices using pre-specified search terms (see Appendix 1).

Those included were adults over 18 years with type 2 diabetes mellitus prescribed either insulins or sulphonylureas, in the 6 months prior to 1st January 2013. The criteria for selection of participants included in the study is detailed in Figure 1. Participants were divided into two cohorts: (i) individuals prescribed insulins with or without other anti-diabetes medication including sulphonylureas; and (ii) those prescribed sulphonylureas with or without other anti-diabetes drugs excluding insulins.

Participants were followed from 1st January 2013 to 31st December 2015. Participants exited the study early when they died or left the dataset. The date at which individuals left was defined as six months after the last prescription of insulins or sulphonylureas or a ‘left’ registration status recorded after the last prescription of either cohort medication. Individuals in the sulphonylurea cohort who commenced insulin after 1st January 2013 were switched to the insulin cohort on the date insulins were first prescribed. Similarly, those individuals prescribed both insulins and sulphonylureas who stopped receiving prescriptions for insulins were switched to the sulphonylurea cohort six months after the last prescription of insulins.

Hypoglycaemia was defined as any recording of one of several specified Read codes for hypoglycaemia (see Appendix 1) or documented blood glucose measurements below 3.9 mmol/L in the EHR. We limited the number of hypoglycaemia episodes to one per day if multiple were recorded. If multiple blood glucose measurements were recorded on the same day, only the lowest was included.

The main exposure was participants’ self-reported ethnicity categorised according to the 2001 UK national Census, and recorded in the EHR using Read codes (Appendix 1). Nine categories of ethnicity were included in the analysis: White British, Other White ethnicities, Indian, Pakistani, Bangladeshi, Other Asian, Black Caribbean, Black African and Other Black ethnicities. Due to substantial heterogeneity, ‘Other’ ethnicities and those who ethnicity were not recorded were excluded from the final analysis.

Participant-level data on other potential confounders were also collected at baseline: age, sex and socioeconomic status (using Townsend Deprivation Index scores). Details of how these were handled in the multivariable models is given in Appendix 2.

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## Statistical Analysis

We calculated crude incidence rates with 95% confidence intervals of all recorded episodes of hypoglycaemia per 1,000 patient-years (PY) for each of the nine categories of ethnicity in each cohort. Using multivariable random effects Poisson regression adjusting for clustering within CCGs, unadjusted and adjusted incidence rate ratios of hypoglycaemia by ethnicity with 95% confidence intervals were calculated in each cohort. White British ethnicity was chosen as the reference category in the Poisson models. Missing data did not exceed 0.2% for any of the co-variables measured (Table 1). Therefore, participants with missing data were excluded from the multivariable models.

There were substantially more people with higher Townsend scores indicating greater deprivation in the study area than the national average. Therefore, quintiles of the study participants’ scores rather than national quintiles were used in the multivariable analyses.(14)

The ethnicities of individuals who died or left the study group after stopping their medications was compared with the entire study population to assess for possible bias.

We used a likelihood ratio test (LRT) to assess the fit of any interaction between cohort medications and the major ethnicities, on hypoglycaemic risk, in a confounder-adjusted model combining both cohorts.

We conducted a sensitivity analysis of the risks of hypoglycaemia associated with ethnic group for three levels of hypoglycaemia based on available blood glucose measurements: all hypoglycaemia defined as any Read code for hypoglycaemia and/or blood glucose measurement below 3.9 mmol/L; moderate-severe hypoglycaemia defined as any Read code for hypoglycaemia and/or blood glucose measurement below 3.5 mmol/L; and severe hypoglycaemia defined as any Read code for hypoglycaemia and/or blood glucose below 3.0 mmol/L (see Appendix 3).

All analyses were undertaken using Stata 14 (StataCorp. Texas, USA).(15)

# Results

Figure 1 displays the numbers of participants included in the study. In the year of data extraction there were a total of 74,867 adults with type 2 diabetes of whom there were 19,771 eligible people on insulin and/or sulphonylureas included in the study; 7,269 and 12,502 were assigned to the insulin and sulphonylurea cohorts respectively.

Table 1 shows the baseline characteristics of the study population. The mean age of all participants was 66.2 years (SD, 13.3 years): 66.7 years (SD, 13.3) and 65.9 years (SD, 13.3) in the insulin and sulphonylurea cohorts respectively. Men accounted for 53.5% of all participants: 50.1% and 55.5% in the insulin and sulphonylurea cohorts respectively.

Most participants were of South Asian ethnicity, 43.4% in the insulin cohort and 49.7% in the sulphonylurea cohort with Bangladeshis comprising the largest majority in both cohorts, 23.8% and 27.3% respectively. White Europeans accounted for 26.8% and 22.9%of the insulin and sulphonylurea cohorts respectively with most identifying as White British: 19.1% and 16.3% of each cohort respectively. Participants identifying with Black African/Caribbean ethnicities formed 25.1% and 22.2% of the insulin and sulphonylurea cohorts. Of these, Black Caribbeans constituted 11.7% and 8.6% and Black Africans 8.0% and 8.9% of the insulin and sulphonylurea cohorts respectively. (Table 1)

Participants contributed a total analysis time of 50,472 years, with an average of 2.55 years per participant. The incidence rates of hypoglycaemia were 50.6 events per 1,000 person-years (95% CI, 47.7,53.8) in the insulin cohort and 25.5 per 1,000 PY (95% CI, 23.7,27.4) in the sulphonylurea cohort.

## Insulin cohort

Figure 2 shows the adjusted incidence rate ratios (IRR) of hypoglycaemia in each cohort. After adjustment for all other co-variables, Black Caribbean participants were at greater risk of hypoglycaemia compared to their White British counterparts, adjusted IRR 1.56 (95% CI, 1.21, 2.01), while Bangladeshis had reduced risk, adjusted IRR 0.49 (95% CI, 0.38, 0.64) (Figure 2). No evidence of differences in hypoglycaemic risk was found between other ethnicities and White British participants prescribed insulins. Tables of the incidence rates, unadjusted and adjusted Poisson regression models can be found in Appendix 3.

## Sulphonylurea cohort

Among those prescribed sulphonylureas, both Black Caribbean and Black African participants had higher risks of hypoglycaemia that White British individuals: adjusted IRR 1.63 (95% CI, 1.15, 2.29) and 1.90 (95% CI, 1.32, 2.75) respectively (Figure 2). Furthermore, we Indian and Other South Asian participants were also at increased hypoglycaemic risk than those identifying as White British: adjusted IRR 1.93 (95% CI, 1.39, 2.69) and 1.73 (95% CI, 1.09, 2.77) respectively (Figure 2). Tables of the incidence rates, unadjusted and adjusted Poisson regression models can be found in Appendix 3.

## Interaction of ethnicity and insulin-use on the risk of hypoglycaemia

In a combined cohort model, there was evidence of interaction between major ethnic group and insulin-use (LRT p = 0.01). Both Indian and Bangladeshi ethnicity diminished the hypoglycaemic risk associated with insulin use versus sulphonylureas by 48.0% (95% CI, 20.5, 66.0) and 47.5% (95% CI, 22.4, 65.4) respectively. The baseline adjusted IRR of hypoglycaemia for insulin-use versus sulphonylureas in White British participants was 2.66 (95% CI, 2.01, 3.52), reduced to 1.38 (95% CI, 1.01,1.91) among Indians and 1.40 (95% CI, 1.06, 1.83) in Bangladeshis. There were no significant differences in the increased hypoglycaemic risk from insulin use among the other ethnic groups compared to White British participants (see Appendix 3).

Of those commencing the study in the sulphonylurea cohort, 1,427 from the nine ethnic groups included in the analysis switched to the insulin cohort on receiving a first prescription of insulins after the 1st January 2013. Similarly, 173 switched from the insulin to the sulphonylurea cohort (see Appendix 3)

During the three-year study period, 593 (8.2%) individuals in the insulin cohort died, and 572 (4.6%) died in the sulphonylurea cohort. In addition, 1,454 (20.0%) from the insulin cohort and 2,991 (23.8%) of the sulphonylurea cohort left their registered GP list or stopped receiving prescriptions of either cohort medications for six months or more prior to the end of the study period. Compared to the total persons in both cohorts entering the study, a larger proportion of those who died were from White British ethnic groups (Appendix 3). There were no substantial differences in the ethnic distribution of those who left the study or stopped their medication for six months or more and those entering the study (Appendix 3).

### Sensitivity analysis

Evidence of increased relative risk of hypoglycaemia among those prescribed insulins identifying as Black Caribbean compared with White British was found for all three models of hypoglycaemia: all hypoglycaemia, moderate-severe hypoglycaemia and severe hypoglycaemia (see Table 2). Furthermore, strong evidence of reduced hypoglycaemic risk found among Bangladeshis prescribed insulins compared to White British was found in all three models. In the sulphonylurea cohort, Indians were at significantly higher risk of hypoglycaemia in all three models. Black Caribbean and African participants were at increased risk of hypoglycaemia in all three models, though only significant in the all hypoglycaemia and moderate-severe hypoglycaemia models. (Table 2).

# Discussion

This study has found that people of Black Caribbean ethnicity with type 2 diabetes prescribed insulins or sulphonylureas are at increased risk of hypoglycaemia compared to their White British counterparts, while Bangladeshi participants had lower risk. Among participants prescribed sulphonylureas, those identifying as Indian, Black Caribbean and Black African were greater risk of hypoglycaemia than White British individuals. Furthermore, Bangladeshi and Indian ethnicity diminished the increased relative hypoglycaemic risk associated with insulin-use compared to sulphonylureas in a combined cohort confounder-adjusted model.

## Strengths and Limitations

To our knowledge, this is the first study examining the differences in hypoglycaemia between ethnic groups with diabetes using GP-recorded primary care data. In comparison to previous studies, we have studied a population with type 2 diabetes only and examined the risks of hypoglycaemia in separate insulin and sulphonylurea cohorts.

Our study had several limitations. During the study period, 22.4% of participants did not complete full follow-up due to leaving the registered GP list or stopping medication for six months or more. However, there were no major differences in the distribution of ethnicities among those who did not complete follow up compared to those entering the study. Thus, though attrition of participants may have reduced the strength of associations observed in this study, it is unlikely to have influenced their direction. Of the 5.9% of participants who died, a larger proportion were of White British ethnicity compared to those entering the study. This may have led to bias in our findings if a substantial proportion of those who died experienced fatal hypoglycaemia. We did not have information on the cause of death and were thus unable to explore this further. However, in both cohorts, participants of White European ethnicity were generally older than the ethnic groups except Black Caribbeans (Appendix 3). Older age, which may partially account for the higher mortality among White British individuals, was adjusted for in the multivariable Poisson regression models estimating hypoglycaemic risk.

This study is subject to the limitations of routinely collected clinical data in which inaccuracies and inconsistencies in the recording of both outcomes and exposures may have led to bias in its findings. We were unable to account for clustering of participants within GP practices, between which diabetes management, including attention to hypoglycaemia, and ethnic group demographics may differ. However, we did cluster participants by the CCG area within which they were registered with their GP practice. This is likely to account for some inter-practice variation due to the shared funding priorities, prescribing practices, infrastructure, secondary care support and demographics of GP practices within each CCG.

We did not have direct access to hospital records and were thus unable to directly capture all hypoglycaemic episodes recorded in hospital settings, only some of which may have been recorded in the GP record. Given that only 4.7% of hypoglycaemia is estimated to be reported to a clinician, previous studies looking at hospital episodes are likely to have captured only the severest cases.(16,17) In contrast, this study used a broader definition of hypoglycaemia to capture a range of severities. Though most Read codes used by primary care clinicians do not indicate the severity of hypoglycaemia experienced, it is likely they refer to symptomatic hypoglycaemia resulting in the assistance of a clinician being sought and hypoglycaemia being recorded. In addition, we also included any documented blood glucose below 3.9 mmo/L. Therefore, our definition of hypoglycaemia accords with the classifications of clinically important and serious hypoglycaemia for use in clinical studies as defined by the American Diabetes Association Workgroup on Hypoglycaemia.(18) To avoid including multiple recordings of a single hypoglycaemic episode, we excluded any additional episodes recorded on the same day.

We did not collect information on dosage or on individuals’ levels of medication adherence so were unable to account for this in the analysis.

## Comparison with other literature

Our results reflect Zaccardi et al who found increased hypoglycaemic risk among Black Caribbeans compared to White British individuals with both type 1 and type 2 diabetes hospitalised in the UK with hypoglycaemia. They found the risk of hypoglycaemia to be lower among Bangladeshis, Indians and Pakistanis.(4) However, we have demonstrated that ethnic differences in hypoglycaemic risk vary according to the type of intensive diabetic treatment used, with lower risk among Bangladeshis prescribed insulins, while Indians and Black Africans prescribed sulphonylureas also had greater hypoglycaemic risk. However, when investigating the impact of ethnicity, the Hospital Episode Statistics (HES) database from which Zaccardi et al drew their data may be less reliable than primary care datasets because up to a half of ethnicity codes recorded at hospital admission have been reported as ‘unknown’ or missing.(19)

Our findings are also consistent with studies of people with diabetes in North America, which have found African Americans to be at higher risk of hypoglycaemia than White European individuals.(6,7,20,21). Karter et al performed a seven-year longitudinal study with type 1 and 2 diabetes prescribed insulin and/or sulphonylureas and found African Americans had consistently higher rates of severe hypoglycaemia than White Europeans, while Latinos and Asians had lower rates.(8)

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## Possible reasons for differences in hypoglycaemic risk among ethnic minority groups

The higher risk of hypoglycaemia found among Black African/Caribbean ethnic groups may be partly explained by relatively intensive glycaemia targets in these ethnic groups. Black African/Caribbean and South Asian ethnic groups tend to have higher HbA1c levels at a given blood glucose than White European counterparts.(22,23) Consequently, these individuals may be at greater risk of hypoglycaemia than White European populations when lowering HbA1c to national and international glycaemic targets.

However, the observed variation in hypoglycaemic risk between the insulin and sulphonylurea cohorts, particularly among Bangladeshis, Indians and Black Africans suggest possible differences in biological and/or cultural responses to insulins and sulphonylureas. For instance, South Asians are known to be less likely to accept insulin and, if prescribed, are more likely to use basal insulins associated with less dramatic falls in blood glucose when administered.(11,12,24) This may provide some explanation for the significant modifying effect of Bangladeshi and Indian ethnicity on the observed hypoglycaemic risk associated with insulin use.

Furthermore, genetic factors impacting on the effectiveness of sulphonylureas between different ethnicities such as poor therapeutic responses among White European participants may also have contributed to the higher relative risk of hypoglycaemia observed among the Black Caribbean, Black African and Indian ethnic groups in the sulphonylurea cohort.(25)

## Conclusions

This study adds to the evidence of variation in propensity to hypoglycaemia by ethnic group. It identified greater hypoglycaemic risk among Black ethnicity populations with type 2 diabetes in primary care who were using either insulins or sulphonylureas as well as higher risks in South Asian versus White European ethnic groups on sulphonylureas. Further investigation of ethnic differences in hypoglycaemia using larger nationally representative primary care datasets is recommended to inform policy on appropriate treatment targets by ethnic group.

# Funding

Manil Malawana received funding from the National Institute of Health Research In Practice Fellowship scheme [NIHR-IPF-15-09-13]. Rohini Mathur is supported by a Sir Henry Wellcome Postdoctoral Fellowship from the Wellcome Trust [201375/Z/16/Z]. Andrew Hutchings was supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North Thames at Bart’s Health NHS Trust. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

# Conflicts of Interest

We declare no conflicts of interest.

# Ethical considerations

This is a secondary analysis of non-identifiable routine primary care data, which is covered by an existing data sharing agreement between the research institution (Clinical Effectiveness Group, Queen Mary University of London) and each General Practice providing routinely collected data. Ethics approval for this study was not required.

# References

1. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal TP, Hemmingsen C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2013;(11):CD008143.

2. Cryer PE. Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia. Diabetes. 2014;63(7):2188–95.

3. Bruderer SG, Bodmer M, Jick SS, Bader G, Schlienger RG, Meier CR. Incidence of and risk factors for severe hypoglycaemia in treated type 2 diabetes mellitus patients in the UK--a nested case-control analysis. Diabetes Obes Metab. 2014;16(9):801–11.

4. Zaccardi F, Webb DR, Davies MJ, Dhalwani NN, Housley G, Shaw D, et al. Risk factors and outcome differences in hypoglycaemia-related hospital admissions: A case-control study in England. Diabetes Obes Metab. 2017 Mar;

5. Shen JJ, Washington EL. Identification of diabetic complications among minority populations. Ethn Dis. 2008;18(2):136.

6. Berkowitz SA, Karter AJ, Lyles CR, Liu JY, Schillinger D, Adler NE, et al. Low socioeconomic status is associated with increased risk for hypoglycemia in diabetes patients: the Diabetes Study of Northern California (DISTANCE). J Health Care Poor Underserved. 2014 May;25(2):478–90.

7. Lopez JMS, Bailey RA, Rupnow MFT. Demographic Disparities Among Medicare Beneficiaries with Type 2 Diabetes Mellitus in 2011: Diabetes Prevalence, Comorbidities, and Hypoglycemia Events. Popul Heal Manag. 2015;18(4):283–9.

8. Karter AJ, Lipska KJ, O’Connor PJ, Liu JY, Moffet HH, Schroeder EB, et al. High rates of severe hypoglycemia among African American patients with diabetes: the surveillance, prevention, and Management of Diabetes Mellitus (SUPREME-DM) network. J Diabetes Complications. 2017 May;31(5):869–73.

9. Williams LK, Padhukasahasram B, Ahmedani BK, Peterson EL, Wells KE, González Burchard E, et al. Differing effects of metformin on glycemic control by race-ethnicity. J Clin Endocrinol Metab. 2014;99(9):3160–8.

10. Davidson JA, Lacaya LB, Jiang H, Heilmann CR, Scism-Bacon JL, Gates JR, et al. Impact of race/ethnicity on the efficacy and safety of commonly used insulin regimens: a post hoc analysis of clinical trials in type 2 diabetes mellitus. Endocr Pr. 2010;16(5):818–28.

11. Verma A, Birger R, Bhatt H, Murray J, Millett C, Saxena S, et al. Ethnic disparities in diabetes management: a 10-year population-based repeated cross-sectional study in UK primary care. J Public Health (Oxf). 2010 Jun;32(2):250–8.

12. Chong E, Wang H, King-Shier KM, Quan H, Rabi DM, Khan NA. Prescribing patterns and adherence to medication among South-Asian, Chinese and white people with type 2 diabetes mellitus: a population-based cohort study. Diabet Med. 2014 Dec;31(12):1586–93.

13. Khan H, Lasker SS, Chowdhury TA. Prevalence and reasons for insulin refusal in Bangladeshi patients with poorly controlled Type 2 diabetes in East London. Diabet Med. 2008 Sep;25(9):1108–11.

14. Hippisley-Cox J. Cut offs for Townsend quintiles in England and Wales and QResearch [Internet]. 2011 [cited 2017 Aug 21]. Available from: http://www.qresearch.org/PowerPointpresentations/Cut offs for Townsend quintiles in England and Wales and QResearch.pdf

15. Stata Statistical Software: Release 14. College Station, Texas: Stata Corp LP; 2015.

16. Mitchell BD, Vietri J, Zagar A, Curtis B, Reaney M. Hypoglycaemic events in patients with type 2 diabetes in the United Kingdom: associations with patient-reported outcomes and self-reported HbA1c. BMC Endocr Disord. 2013;13:59.

17. AJ K, HH M, JY L, KJ L. Surveillance of hypoglycemia—limitations of emergency department and hospital utilization data. JAMA Intern Med [Internet]. 2018 Apr 16; Available from: http://dx.doi.org/10.1001/jamainternmed.2018.1014

18. on Hypoglycemia ADA. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28(5):1245–9.

19. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, VanStaa T, Grundy E, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. J Public Health (Oxf). 2014 Dec;36(4):684–92.

20. Miller ME, Bonds DE, Gerstein HC, Seaquist ER, Bergenstal RM, Calles-Escandon J, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ. 2010;340:b5444.

21. Emons MF, Bae JP, Hoogwerf BJ, Kindermann SL, Taylor RJ, Nathanson BH. Risk factors for 30-day readmission following hypoglycemia-related emergency room and inpatient admissions. BMJ Open Diabetes Res Care. 2016;4(1):e000160.

22. Herman WH, Dungan KM, Wolffenbuttel BHR, Buse JB, Fahrbach JL, Jiang H, et al. Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes. J Clin Endocrinol Metab. 2009 May;94(5):1689–94.

23. Wolfenbuttel BH, Herman WH, Gross JL, Dharmalingam M, Honghua HJ, Hardin DS. Ethnic Differences in Glycemic Markers in Patients With Type 2 Diabetes. Diabetes Care. 2013;36(October):2931–6.

24. Close CF, Lewis PG, Holder R, Wright AD, Nattrass M. Diabetes care in South Asian and white European patients with type 2 diabetes. Diabet Med. 1995 Jul;12(7):619–21.

25. Loganadan NK, Huri HZ, Vethakkan SR, Hussein Z. Genetic markers predicting sulphonylurea treatment outcomes in type 2 diabetes patients: current evidence and challenges for clinical implementation. Pharmacogenomics J. 2016 Jun;16(3):209–19.

**Tables:**

Table 1. Baseline statistics for participants in the insulin and sulphonylurea cohorts at the onset of the study.

|  |  |  |
| --- | --- | --- |
|  | Insulins | Sulphonylureas |
|  | N  (%) | N  (%) |
| Total | 7,269  100 | 12,502  (100) |
| Ethnicities |  |  |
| White British | 1387  (19.1) | 2037  (16.3) |
| Other White | 558  (7.7) | 829  (6.6) |
| Indian | 728  (10.0) | 1,409  (11.3) |
| Pakistani | 472  (6.5) | 861  (6.9) |
| Bangladeshi | 1,732  (23.8) | 3,415  (27.3) |
| Other Asian | 226  (3.1) | 519  (4.2) |
| Caribbean | 853  (11.7) | 1,076  (8.6) |
| African | 579  (8.0) | 1,109  (8.9) |
| Other Black ethnicities | 259  (3.6) | 431  (3.5) |
| Other ethnicities | 428  (5.9) | 738  (5.9) |
| Not recorded | 47  (0.7) | 78  (0.6) |
| Age categories |  |  |
| <55 | 1,297  (17.8) | 2,576  (20.6) |
| 55-64 | 1,910  (26.3) | 3,451  (27.6) |
| 65-74 | 1,815  (25) | 2,930  (23.4) |
| 75+ | 2,247  (30.9) | 3,545  (28.4) |
| Gender |  |  |
| Female | 3,624  (49.9) | 5,566  (44.5) |
| Male | 3,645  (50.1) | 6,936  (55.5) |
| Townsend Quintiles |  |  |
| 1. -5.65 - 3.45 | 1,399  (19.3) | 2,524  (20.2) |
| 2. 3.46 - 4.57 | 1,430  (19.7) | 2,442  (19.6) |
| 3. 4.58 - 5.43 | 1,485  (20.5) | 2,530  (20.3) |
| 4. 5.44 - 6.08 | 1,470  (20.3) | 2,500  (20) |
| 5. 6.09 - 8.99 | 1,477  (20.3) | 2,482  (19.9) |
| Missing | 8  (0.1) | 24  (0.2) |

Table 2. Adjusted incidence rate ratios of all (blood glucose <3.9 mmol/L and Read code for hypoglycaemia), moderate-severe (blood glucose <3.5 mmol/L and Read code for hypoglycaemia) and severe (blood glucose <3.0 mmol/L and Read code for hypoglycaemia) hypoglycaemia by ethnicity in insulin and sulphonylurea cohorts, adjusting for age, gender, socioeconomic status and clustering within Clinical Commissioning Groups. D = number of hypoglycaemia events

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Insulin | | | Sulphonylureas | | |
|  | All hypoglycaemia | Moderate-severe hypoglycaemia | Severe hypoglycaemia | All hypoglycaemia | Moderate-severe hypoglycaemia | Severe hypoglycaemia |
|  | Adj. IRR  [95% CI] | Adj. IRR  [95% CI] | Adj. IRR  [95% CI] | Adj. IRR  [95% CI] | Adj. IRR  [95% CI] | Adj. IRR  [95% CI] |
| Ethnic group | D = 969 | D = 792 | D = 649 | D = 712 | D = 499 | D = 346 |
| White British | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] | 1.00 [Reference] |
| Other White | 0.75 [0.53,1.06] | 0.78 [0.54,1.14] | 0.82 [0.54,1.23] | 1.08 [0.70,1.65] | 1.21 [0.74,1.98] | 1.46 [0.83,2.57] |
| Indian | 1.02 [0.76,1.37] | 0.91 [0.65,1.28] | 0.81 [0.56,1.19] | 1.93\*\*\* [1.39,2.69] | 2.02\*\*\* [1.35,3.00] | 1.67\* [1.02,2.73] |
| Pakistani | 0.94 [0.66,1.34] | 0.81 [0.54,1.21] | 0.67 [0.42,1.08] | 1.26 [0.83,1.91] | 1.31 [0.79,2.17] | 1.17 [0.62,2.19] |
| Bangladeshi | 0.49\*\*\* [0.38,0.64] | 0.49\*\*\* [0.36,0.65] | 0.50\*\*\* [0.37,0.69] | 1.02 [0.76,1.38] | 1.12 [0.78,1.59] | 1.38 [0.91,2.08] |
| Other South Asian | 1.45 [0.94,2.24] | 1.10 [0.66,1.83] | 0.81 [0.43,1.50] | 1.73\* [1.09,2.77] | 1.44 [0.79,2.64] | 0.90 [0.40,2.05] |
| Caribbean | 1.56\*\*\* [1.21,2.01] | 1.53\*\* [1.16,2.03] | 1.46\* [1.07,2.00] | 1.63\*\* [1.15,2.29] | 1.56\* [1.04,2.34] | 1.54 [0.95,2.50] |
| African | 1.10 [0.80,1.52] | 0.91 [0.63,1.31] | 0.76 [0.49,1.16] | 1.90\*\*\* [1.32,2.75] | 1.96\*\* [1.26,3.04] | 1.59 [0.91,2.78] |
| Other Black ethnicities | 0.94 [0.59,1.49] | 0.69 [0.39,1.20] | 0.54 [0.28,1.04] | 1.06 [0.59,1.92] | 0.91 [0.44,1.91] | 0.75 [0.29,1.96] |

Exponentiated coefficients; 95% confidence intervals in brackets

\* *p* < 0.05, \*\* *p* < 0.01, \*\*\* *p* < 0.001

**Figures:**

Figure 1. Flowchart of patients selected for inclusion in the study analysis

Excluded

No recorded prescription of sulphonylureas or insulin within 6 months prior to 1st January 2013.

(n = 48,353)

\*Excluding non-melanoma skin cancers

Prescribed Insulin 5th July to 31st December 2012.

(n=7,269)

Prescribed Sulphonylureas without insulin5th July to 31st December 2012.

(n=12,502)

Excluded

No history of oral antidiabetic medication use – possible miscoded type 1 diabetes.

(n = 415)

Prescribed Sulphonylureas and/or Insulin during the 6-month period prior to 1st January 2013

(n=19,771)

Excluded

History of cancer\* or on palliative care register?

(n = 6,312)

Excluded

Confidential patients (data access denied)

(n = 16)

Patients over 18 years with Type 2 Diabetes registered with a GP for at least 1 year prior to 1st Jan 2013.

(n = 74,867)

Figure 2. Incidence rate ratios of hypoglycaemia in nine ethnic groups and adjusting for age, gender, socioeconomic status and clustering within Clinical Commissioning Groups: (a) insulin cohort; (b) sulphonylurea cohort.

