Prevalence and Incidence of Hypoglycaemia in 532,542 People with Type 2 Diabetes on Oral Therapies and Insulin: A Systematic Review and Meta-Analysis of Population Based Studies

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Abstract

Objective
To collate and evaluate the current literature reporting the prevalence and incidence of hypoglycaemia in population based studies of type 2 diabetes.

Research Design and Methods
Medline, Embase and Cochrane were searched up to February 2014 to identify population based studies reporting the proportion of people with type 2 diabetes experiencing hypoglycaemia or rate of events experienced. Two reviewers independently screened studies for eligibility and extracted data for included studies. Random effects meta-analyses were carried out to calculate the prevalence and incidence of hypoglycaemia.

Results
46 studies (n = 532,542) met the inclusion criteria. Prevalence of hypoglycaemia was 45% (95% CI 0.34,0.57) for mild/moderate and 6% (95% CI, 0.05,0.07) for severe. Incidence of hypoglycaemic episodes per person-year for mild/moderate and for severe was 19 (95% CI 0.00, 51.08) and 0.80 (95%CI 0.00,2.15), respectively. Hypoglycaemia was prevalent amongst those on insulin; for mild/moderate episodes the prevalence was 50% and incidence 23 events per person-year, and for severe episodes the prevalence was 21% and
incidence 1 event per person-year. For treatment regimes that included a sulphonylurea, mild/moderate prevalence was 30% and incidence 2 events per person-year, and severe prevalence was 5% and incidence 0.01 events per person-year. A similar prevalence of 5% was found for treatment regimes that did not include sulphonylureas.

Conclusions
Current evidence shows hypoglycaemia is considerably prevalent amongst people with type 2 diabetes, particularly for those on insulin, yet still fairly common for other treatment regimes. This highlights the subsequent need for educational interventions and individualisation of therapies to reduce the risk of hypoglycaemia.

Introduction
Hypoglycaemia in type 2 diabetes is associated with a considerable cost and burden to the health service, with an estimated annual cost to the NHS of £39 million[1]. There can also be substantial consequences for the individual, with an increased risk of mortality and morbidity from severe episodes [2–4]. Hypoglycaemia significantly impacts on an individual’s quality of life, their employment, social interactions, and driving [5–7]. In addition to the direct effects of hypoglycaemia, there may be a substantial indirect impact on serious long-term health consequences from medication non-adherence and purposeful hyperglycaemia, due to fear and avoidance of hypoglycaemia [8].

A common cause of hypoglycaemia is iatrogenic [9]. In order to avoid long-term complications of type 2 diabetes, emphasis is placed on improving blood glucose control [9–11]. A recent meta-analysis revealed that intensive glycaemic control in people with type 2 diabetes can result in a 17% reduction in non-fatal myocardial infarction and a 15% reduction in coronary heart disease events [12]. To help achieve tight glycaemic control, people with type 2 diabetes are frequently placed on intensive treatment regimens, including earlier initiation of insulin. Intensive regimens and tighter glycaemic control have been shown to increase the risk of hypoglycaemia[13–15]. However, the topic of glycaemic management and pharmacological treatments is becoming more complex. Newer therapies and more treatment combinations, are increasingly becoming available, with the aim of maximising glucose control without the increased risk of hypoglycaemia[9, 16].

In addition to treatment regimes, other currently identified potential risk factors for hypoglycaemia in type 2 diabetes include exercise [17], increased age [18], presence of co-morbidities [18], hypoglycaemia unawareness [18], dietary mistakes [19], excessive dieting [20] or weight loss, alcohol [21], number of years since diabetes diagnosis [22], and time since insulin initiated [23],

Hypoglycaemia prevalence in real world type 2 diabetes settings has been considered [3, 24], however, there has not been a systematic review and meta-analyses of the literature. Previously published systematic reviews that have considered hypoglycaemic episodes in type 2 diabetes have tended to focus on clinical trials of the safety and efficacy of a particular drug [15, 25–30]. Clinical trials usually exclude participants at higher risk of hypoglycaemia, attract more motivated and selective participants, have a treat to target design and place participants on treatment regimens specifically for the study. Consequently, generalisability of findings to real world settings may be limited and hypoglycaemia prevalence and incidence in clinical trials may be lower than in clinical practice. Knowing the incidence of hypoglycaemia is
important to provide insight into its impact both clinically and from a patient level. It enables
the planning of resources, exploration of risk factors and design of interventions for prevention
of hypoglycaemia. Additionally, the frequency and severity of hypoglycaemia is often used as a
rationale for the use of newer treatments and as a clinical indicator for the choice of treatment
patients are placed on.

To our knowledge, there have been no systematic reviews of the prevalence or incidence
rates of hypoglycaemic events in type 2 diabetes in population based studies. This systematic
review aimed to collate and evaluate the current literature reporting the prevalence (proportion
of people) and the incidence (rate of episodes) of hypoglycaemia in a real world type 2 diabetes
population.

Methods
Search Strategy and Study Selection

We searched electronic bibliographic databases Ovid Medline (including in-process and other
non-indexed citations) and Embase from 1998 to February 2014 and Cochrane (issue 2, 2014),
using a combination of keywords and MeSH terms with English and American spellings. The
search terms used covered type 2 diabetes, hypoglycaemia prevalence and hypoglycaemia inci-
dence. An example search strategy tailored for Ovid medline can be found in S1 Fig.

The primary aim of this systematic review was to explore the incidence and prevalence of
hypoglycaemia in people with type 2 diabetes within a general population-based setting. We in-
cluded observational studies where: 1) the study population were a defined general population
sampled from either a defined geographical location, attendees at a primary, secondary or
other healthcare centre, or people registered on a health service or health insurance database;
2) the study population (or sub-population) all had type 2 diabetes and were aged \( \geq 18 \) years
old; 3) they were published in English language; and 4) they were published as full papers. We
additionally required studies to report the number of type 2 diabetes participants who had
experienced \( \geq 1 \) hypoglycaemic episode, the incidence of hypoglycaemic episodes experienced,
or data to allow the calculation of one of these measures. We did not apply any restrictions re-
lating to the classification, definition or measurement of how hypoglycaemia was utilised by
studies. We excluded studies if: 1) they were pharmacological trials or the study methods in-
volved any alteration to a participant’s treatment or care, either pharmacological or beha-
vioural; 2) the majority of participants were pregnant, fasting, on a restrictive diet, or were
selected on the basis of having a specific acute or chronic illness; 3) participants were selected
on the basis of their hypoglycaemia history or recent initiation of treatment regime; 4) partici-
pants were sampled via an established survey/consumer panel or a consumer database; or 5)
hypoglycaemia rates were solely reported over less than one week.

Following removal of duplicate publications, titles and abstracts were reviewed indepen-
dently by two reviewers (CE, TR) in order to identify studies that met the inclusion criteria.
Where it was unclear from the abstract whether the inclusion criteria were met, the full article
was retrieved and reviewed. In instances where there were disagreements between reviewers, a
third reviewer (AJD or KK) was consulted.

Data extraction

A data extraction form was developed and pilot tested, with adaptations made accordingly.
Two reviewers (CE, TR) extracted independently from included studies.

Where data were available, we extracted the following for each study: 1) study details (in-
cluding study design, year published and country); 2) population details (including sample
source, mean age, ethnicity, mean HbA1c, sex,treatment regimens and cardiovascular disease
or events); 3) methods used to measure hypoglycaemia (self-report questionnaires, prospective diaries, emergency department admission records, claims databases); 4) the time period hypoglycaemia was measured over; and 5) severity measured (definition given by the study). We extracted outcome data for the proportion of T2DM participants only who had experienced at least one hypoglycaemic episode (prevalence) and the incidence rate of episodes experienced (or data to calculate).

Quality assessment

We created a quality assessment tool using elements from the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies [31], the Cochrane Collaboration Risk of Bias Tool [32] and the Quality assessment tool for systematic reviews of Observational Studies (QATSO) [33], see S1 Table. Two reviewers (CE, TR) independently assessed all studies for methodological quality. Each criterion was given a score of ++, + or -, and an overall quality grade was assigned for each of the following; sample bias (sample source representative and described well, sampling method, eligibility criteria applied and described, sufficient sample response), data collection bias (data collection tool well described, measurement reliability) and confounding and explanatory factors considered.

Data synthesis

For analytic and descriptive purposes, we categorised and defined hypoglycaemia by severity of the episode measured within the study. Where possible, based on the description given in the paper, studies were categorised as either mild/moderate or severe. Mild/moderate hypoglycaemia was referred to by studies when no third party assistance was needed during a hypoglycaemic episode. Severe hypoglycaemia was used by studies when third party assistance was required. However, some studies did not specify a severity when gathering some or all of the hypoglycaemia data; these data were classified as “unspecified” hypoglycaemia. It was assumed that the “unspecified” data covered both severe and mild/moderate hypoglycaemia. Where a study reported data separately for more than one of the classifications (severe, mild/moderate and unspecified), we extracted and analysed the data separately. If a study reported zero hypoglycaemic events, we entered 0.001 into the meta-analysis to avoid the study being excluded [32]. Where two prevalence or incidence means were reported in a paper for different populations, the pooled mean was calculated [32]. Population treatment categories relating to hypoglycaemia prevalence and incidence, were based on the available data. Where possible, data were grouped into: insulin, with or without oral-glucose lowering therapies; sulphonylureas, non-insulin but with or without other oral-glucose lowering therapies; non-sulphonylureas, non-insulin and non sulphonylurea oral-glucose lowering therapies; or mixed oral-glucose lowering therapies, non-insulin but no further description given relating to type of oral-glucose lowering therapies. For studies where treatment categories were not mutually exclusive, if the whole population were pharmacologically controlled, data for insulin were subtracted from the overall data, where possible, and the remaining data were grouped in the mixed oral glucose lowering category.

For the primary outcome of interest (the proportion of people who had experienced hypoglycaemia), we conducted meta-analyses for mild/moderate episodes, severe episodes and unspecified episodes. We carried out sub-analyses within these categories by treatment regime of the population. We also carried out a sub-analysis for severe hypoglycaemia which specifically required emergency or medical assistance. We used meta-regression techniques to assess the following potential explanatory variables at the study-level: mean age, percentage of male participants, mean HbA1c level, and the time over which hypoglycaemia was measured.
We carried out further meta-analyses for the rate of hypoglycaemic episodes per person year, for the three categories of, mild/moderate, severe and unspecified. Again, analyses were stratified by therapy option.

When calculating confidence intervals for meta-analyses, negative values can be found. We decided to cap all confidence intervals at 0.00, due to it not being plausible to have a negative confidence interval for prevalence or incidence.

Heterogeneity was assessed using the \( I^2 \) statistic. Due to high levels of heterogeneity, we used random-effects models throughout to calculate effect sizes. Publication bias was assessed with a funnel plot and the Egger test. This was carried out separately for studies reporting, mild/moderate, severe and unspecified events and separately for prevalence and incidence. Significance was set at \( P<0.05 \), all \( p \)-values are two-sided and 95% confidence intervals are quoted throughout. We performed all analyses in Stata version 13 (StataCorp, College Station, TX).

**Results**

**Identification of studies**

Results relating to the identification process for eligible studies are summarised in Fig 1. Searches yielded 3348 citations, and 3063 unique titles and abstracts were screened for eligibility. Following full text retrieval of 285 potentially relevant papers, 239 were subsequently excluded, leaving 46 papers eligible for inclusion in the analyses.

**Summary of included studies**

Descriptive characteristics including the definitions and descriptions of hypoglycaemia used by the 46 studies included in the systematic review are summarised in Table 1. All studies were observational, with 27 being cross-sectional, 11 prospective, 6 retrospective and 2 used a mixed methods design of cross-sectional/prospective \( (n = 1) \) or cross-sectional/retrospective \( (n = 1) \). Papers included were published from 1998 to 2013 inclusive. The number of participants within each study ranged from 41 to 361,210. Studies were conducted in Europe \( (n = 25) \), North America \( (n = 14) \), Australia \( (n = 2) \), and Eastern/South East Asia \( (n = 5) \). Ethnicity was poorly reported; of the 9 \( (19.6\%) \) studies that reported ethnicity, the proportion of non-white participants ranged from 17% to 100%. Population samples were obtained from either health clinic attendees \( (n = 21) \), diabetes registries/databases \( (n = 8) \), health insurance databases \( (n = 7) \), emergency department records \( (n = 4) \), community populations \( (n = 3) \) or pharmacy records \( (n = 2) \).

Over half of the studies reported only severe hypoglycaemia \( (n = 24) \), while 3 studies reported severe and mild/moderate. There were 6 studies which reported data on unspecified hypoglycaemia, 8 which reported data on unspecified hypoglycaemia along with severe, and 5 which reported data on unspecified, mild/moderate and severe. For studies reporting the prevalence of hypoglycaemia, the time period used for recall of previous hypoglycaemic episodes ranged from 1 month to 22 years. The majority of studies \( (n = 17) \) measured episodes over a period of 12 months. The measurement period for studies reporting the incidence of hypoglycaemia, ranged from 1 week to 22 years. The most frequently used was 12 months \( (9/21) \). A variety of methods/sources, either alone or in combination, were utilised to obtain relevant data. These included questionnaires \( (n = 25) \), emergency department records \( (n = 7) \), prospective diaries \( (n = 4) \), and claims databases \( (n = 3) \).
Study quality

A breakdown of study quality is presented in S1 Table. Most studies received a high quality grading for the consideration of data collection bias (42/46, 91.3%) and confounding and
<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Data Source (Hypo info)</th>
<th>Country</th>
<th>Sample size</th>
<th>Male %</th>
<th>Mean HbA1c% (mmol)</th>
<th>CVD events</th>
<th>Hypo: No hypo</th>
<th>Non-white %</th>
<th>Mean Age (years)</th>
<th>Sampling method</th>
<th>Sample source</th>
<th>Design</th>
<th>Length of therapy (years)</th>
<th>Time hypo measured over</th>
<th>Hypo definition</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akram 2006</td>
<td>Questionnaire/Recall</td>
<td>Denmark</td>
<td>401</td>
<td>58</td>
<td>8.3 (67.2)</td>
<td>No hypo</td>
<td>NR</td>
<td>58</td>
<td>66 (median)</td>
<td>Consecutive</td>
<td>Health clinic</td>
<td>Cross-sectional</td>
<td>7 (median) (insulin)</td>
<td>1 Year</td>
<td>Need for assistance</td>
<td>Severeb</td>
</tr>
<tr>
<td>Allen 2004</td>
<td>Prospective Diary</td>
<td>UK</td>
<td>41</td>
<td>63.4</td>
<td>NR</td>
<td>No hypo</td>
<td>NR</td>
<td>NR</td>
<td>66 (median)</td>
<td>Consecutive</td>
<td>Health clinic</td>
<td>Prospective</td>
<td>1.4 (mean) (insulin)</td>
<td>3 Months</td>
<td>Required glucose/</td>
<td>Mildb, Severeb</td>
</tr>
<tr>
<td>Andel 2008</td>
<td>Questionnaire/Recall/Diary</td>
<td>Central/ Eastern europe</td>
<td>8,231</td>
<td>47.3</td>
<td>7.7 (60.7)</td>
<td>No hypo</td>
<td>NR</td>
<td>58</td>
<td>62.2</td>
<td>Consecutive</td>
<td>Health clinic</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>1 Year</td>
<td>Local clinical standards + guidelines</td>
<td>Severeb</td>
</tr>
<tr>
<td>Aung 2011</td>
<td>Questionnaire/Recall</td>
<td>UK</td>
<td>10,66</td>
<td>51</td>
<td>7.3 (56.3)</td>
<td>No hypo</td>
<td>NR</td>
<td>58</td>
<td>67.9</td>
<td>Random</td>
<td>Diabetes registry</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>1 Year</td>
<td>Need for assistance</td>
<td>Severeb</td>
</tr>
<tr>
<td>Bourdelmarch-hasson 2007</td>
<td>Questionnaire/Recall</td>
<td>France</td>
<td>2,832</td>
<td>60.6</td>
<td>7.1 (54.1)</td>
<td>No hypo</td>
<td>NR</td>
<td>63.8</td>
<td>Random</td>
<td>Consecutive</td>
<td>Health insurance database (national)</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>1 Year</td>
<td>Need for assistance</td>
<td>Severeb</td>
</tr>
<tr>
<td>Chan 2010</td>
<td>Questionnaire/Recall</td>
<td>Asia</td>
<td>2,257</td>
<td>49.4</td>
<td>7.5 (58.5)</td>
<td>No hypo</td>
<td>NR</td>
<td>NR</td>
<td>65</td>
<td>Consecutive</td>
<td>Health clinic attendees (outpatients, multicentre)</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>6 Months</td>
<td>Level of assistance/interruption to activities</td>
<td>Unspecified, Mildb, Severeb</td>
</tr>
<tr>
<td>Davis 2005</td>
<td>Questionnaire/Recall</td>
<td>UK</td>
<td>590</td>
<td>58</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>65</td>
<td>Stratified</td>
<td>Health clinic records or from previous study</td>
<td>Cross-sectional</td>
<td>Not reported for the study cohort included for hypoglycaemia</td>
<td>3 Months</td>
<td>Level of symptoms, behaviour, assistance</td>
<td>Unspecified, Mildb, Severeb</td>
</tr>
<tr>
<td>Davis 2010</td>
<td>Questionnaire/Recall</td>
<td>Australia</td>
<td>616</td>
<td>52.3</td>
<td>NR</td>
<td>NR</td>
<td>67</td>
<td>Non-random</td>
<td>Community population (particular geographical location)</td>
<td>Prospective</td>
<td>Diagnosed by health service</td>
<td>NR</td>
<td>6.4 months (Mean)</td>
<td>Severeb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donnelly 2004</td>
<td>Prospective Diary</td>
<td>UK</td>
<td>173</td>
<td>53</td>
<td>8.9 (73.8)</td>
<td>No hypo</td>
<td>NR</td>
<td>65</td>
<td>Random</td>
<td>Prospective</td>
<td>Diabetes registry/database (1 geographical location)</td>
<td>Prospective</td>
<td>NR</td>
<td>1 Month</td>
<td>Need for assistance</td>
<td>Unspecified, Mildb, Severeb</td>
</tr>
<tr>
<td>Green 2012</td>
<td>Questionnaire/Recall</td>
<td>USA</td>
<td>3,000</td>
<td>40.4</td>
<td>Heart Disease</td>
<td>31% (22%)</td>
<td>NR</td>
<td>NR</td>
<td>65</td>
<td>Stratified</td>
<td>Community population (postcode defined)</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>1 Year</td>
<td>Low BG</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Gultek 1999</td>
<td>Questionnaire/Recall</td>
<td>Turkey</td>
<td>114</td>
<td>44.7</td>
<td>NR</td>
<td>58.9</td>
<td>Undear</td>
<td>NR</td>
<td>65</td>
<td>Retrospective</td>
<td>Health clinic attendees (outpatients, single centre)</td>
<td>Retrospective</td>
<td>NR</td>
<td>3.33 years (mean)</td>
<td>Hdp needed due to neuroglycopenia/required parenteral glucose</td>
<td>Severeb</td>
</tr>
<tr>
<td>Henderson 2003</td>
<td>Questionnaire/Recall</td>
<td>UK</td>
<td>215</td>
<td>8.5</td>
<td>8.6 (70.5)</td>
<td>No hypo</td>
<td>NR</td>
<td>NR</td>
<td>Random</td>
<td>Consecutive</td>
<td>Health clinic attendees (outpatients, diabetes clinic, single centre)</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>1 Year</td>
<td>Required glucose/glucagon, level of assistance</td>
<td>Unspecified, Mildb, Severeb</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Data Source (Hypo info)</th>
<th>Country</th>
<th>Sample size</th>
<th>Male %</th>
<th>Mean HbA1c% mmol</th>
<th>CVD events Hypo: No hypo</th>
<th>Non-white %</th>
<th>Mean Age (years)</th>
<th>Sampling method</th>
<th>Sample source</th>
<th>Design</th>
<th>Length of therapy (years)</th>
<th>Time hypo measured over</th>
<th>Hypo definition</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holstein 2003</td>
<td>Emergency records</td>
<td>Germany</td>
<td>9,000</td>
<td>NR</td>
<td>NR</td>
<td>All patients included that met inclusion criteria</td>
<td>NR</td>
<td>NR</td>
<td>Emergency records from one geographical location</td>
<td>Prospective</td>
<td>NR</td>
<td>4 Years</td>
<td>Required intravenous glucose/glucagon. Confirmed BG.</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Honkasalo 2011</td>
<td>Questionnaire/Recall/Emergency dep records</td>
<td>Finland</td>
<td>1,065</td>
<td>NR</td>
<td>NR</td>
<td>All participants eligible invited</td>
<td>NR</td>
<td>NR</td>
<td>Health insurance database (2 geographical locations)</td>
<td>Cross-sectional/Retrospective</td>
<td>NR</td>
<td>1 Year</td>
<td>Need for assistance</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Johnston 2012</td>
<td>Claims database</td>
<td>USA</td>
<td>361,210</td>
<td>51.6</td>
<td>NR</td>
<td>Ischaemic heart disease 26%: 19%</td>
<td>NR</td>
<td>NR</td>
<td>Diabetes registry/database (primary care centres)</td>
<td>Retrospective</td>
<td>NR</td>
<td>1 Year</td>
<td>Need for assistance</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Katon 2013</td>
<td>Emergency dep records/Health insurer</td>
<td>USA</td>
<td>4,117</td>
<td>51.9</td>
<td>NR</td>
<td>19.9</td>
<td>69.4</td>
<td>NR</td>
<td>All patients included that met inclusion criteria</td>
<td>Prospective</td>
<td>NR</td>
<td>5 Years</td>
<td>Emergency visit or hospitalisation</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Kinacova 2012</td>
<td>Emergency records</td>
<td>Czech Republic</td>
<td>37,459</td>
<td>NR</td>
<td>NR</td>
<td>All patients included that met inclusion criteria</td>
<td>Emergency records from one geographical location</td>
<td>Prospective</td>
<td>NR</td>
<td>1 Year</td>
<td>Assistance of emergency services</td>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lecomte 2008</td>
<td>Questionnaire/Recall</td>
<td>France</td>
<td>3,324</td>
<td>53.8</td>
<td>NR</td>
<td>Consecutive</td>
<td>NR</td>
<td>NR</td>
<td>Health insurance database</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>2 Year</td>
<td>Need for assistance</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Leese 2003</td>
<td>Emergency records</td>
<td>UK</td>
<td>7,678</td>
<td>52</td>
<td>NR</td>
<td>65.8</td>
<td>69.4</td>
<td>NR</td>
<td>All patients included that met inclusion criteria</td>
<td>Diabetes registry/database (1 geographical location)</td>
<td>Prospective</td>
<td>NR</td>
<td>3 Year</td>
<td>BG &lt; 3.5 mmol/L - glucose/glucagon needed</td>
<td>Severe</td>
</tr>
<tr>
<td>Leiter 2005</td>
<td>Questionnaire/Recall</td>
<td>Canada</td>
<td>133</td>
<td>NR</td>
<td>7.52 (58.5)</td>
<td>Ischaemic heart disease 27%: 15% Congrescetive heart failure 12%: 6% Cardiovascular disease 83%: 63%</td>
<td>NR</td>
<td>99.9</td>
<td>Convenience</td>
<td>Health clinic attendees (multcentre)</td>
<td>Cross-sectional</td>
<td>10.2</td>
<td>1 month/1 year</td>
<td>BG &lt; 4.0 mmol/L or &lt; 2.8 with assistance</td>
<td>Mild*, Severe</td>
</tr>
<tr>
<td>Lin 2012</td>
<td>Claims database/Health insurer</td>
<td>Taiwan</td>
<td>15,404</td>
<td>45.1</td>
<td>NR</td>
<td>Ischaemic heart disease 27%: 15% Congrescetive heart failure 14%: 6% Cardiovascular disease 9%: 4% Myocardial infarction 9%: 6%</td>
<td>100</td>
<td>64.2</td>
<td>Random</td>
<td>Health insurance database (national)</td>
<td>Retrospective</td>
<td>NR</td>
<td>2 Years</td>
<td>Medical assistance required</td>
<td>Severe</td>
</tr>
<tr>
<td>Lipica 2013</td>
<td>Questionnaire/Recall</td>
<td>USA</td>
<td>9,094</td>
<td>50</td>
<td>7.5 (58.5)</td>
<td>Congrescetive heart failure 14%: 6% Cardiovascular disease 9%: 4% Myocardial infarction 9%: 6%</td>
<td>74.3</td>
<td>59.5</td>
<td>Stratified random</td>
<td>Diabetes registry/database (1 geographical location)</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>1 Year</td>
<td>All patients</td>
<td>Severe</td>
</tr>
<tr>
<td>Lundkvist 2005</td>
<td>Questionnaire/Recall</td>
<td>Sweden</td>
<td>309</td>
<td>60</td>
<td>NR</td>
<td>Macro (mean complications) 0.24:0.25</td>
<td>NR</td>
<td>65</td>
<td>Convenience</td>
<td>Health clinic attendees (7 centres)</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>2 Year</td>
<td>Level of assistance or BG &lt; 3.3 mmol/L</td>
<td>Unspecified, Severe</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Data Source (Hypo info)</th>
<th>Country</th>
<th>Sample size</th>
<th>Male %</th>
<th>Mean HbA1c%</th>
<th>CVD events</th>
<th>Non-white %</th>
<th>Mean Age (years)</th>
<th>Sampling method</th>
<th>Sample source</th>
<th>Design</th>
<th>Length of therapy (years)</th>
<th>Time hypo measured over</th>
<th>Hypo definition</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maggi 2013</td>
<td>Questionnaire/Recall</td>
<td>Italy</td>
<td>1,342</td>
<td>52.5</td>
<td>7.2 (55.2)</td>
<td>No hypo</td>
<td>NR</td>
<td>73.3</td>
<td>Consecutive</td>
<td>Health clinic attendees (57 diabetes centres)</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>3 Months</td>
<td>Requiring hospitalisation</td>
<td>Unspecified, Severe</td>
</tr>
<tr>
<td>McCoy 2012</td>
<td>Questionnaire/Recall</td>
<td>USA</td>
<td>797</td>
<td>NR</td>
<td>NR</td>
<td>Consenience</td>
<td>NR</td>
<td>NR</td>
<td>Cross-sectional</td>
<td>Health clinic attendees (diabetes clinic, single centre)</td>
<td>NR</td>
<td>6 Months</td>
<td>Level of symptoms, assistance</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>McCoy 2013</td>
<td>Questionnaire/Recall</td>
<td>USA</td>
<td>326</td>
<td>53.1</td>
<td>7.6 (59.6)</td>
<td>All patients included that met inclusion criteria</td>
<td>NR</td>
<td>67.1</td>
<td>Cross-sectional</td>
<td>Diabetes registry/database (1 geographical location)</td>
<td>NR</td>
<td>6 Months</td>
<td>Level of symptoms, assistance</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Miller 2001</td>
<td>Questionnaire/Recall</td>
<td>USA</td>
<td>1,055</td>
<td>28.2</td>
<td>7.6 (59.6)</td>
<td>All patients who met inclusion criteria and had sufficient data included</td>
<td>NR</td>
<td>93.8</td>
<td>Cross-sectional</td>
<td>Health clinic attendees (diabetes clinic, single centre)</td>
<td>NR</td>
<td>3.17 Months (mean)</td>
<td>Symptoms, behaviour, need for assistance or glucose &lt;3.3mmol/L</td>
<td>Unspecified, Severe</td>
<td></td>
</tr>
<tr>
<td>Murata 2004</td>
<td>Prospective Diary</td>
<td>USA</td>
<td>344</td>
<td>NR</td>
<td>NR</td>
<td>Random</td>
<td>NR</td>
<td>NR</td>
<td>Prospective</td>
<td>Pharmacy records (3 centres)</td>
<td>NR</td>
<td>11 Months (mean)</td>
<td>BG&lt;3.3mmol/L</td>
<td>Unspecified</td>
<td></td>
</tr>
<tr>
<td>Neil 2007</td>
<td>Questionnaire/Recall</td>
<td>USA</td>
<td>5,965</td>
<td>NR</td>
<td>NR</td>
<td>All participants eligible invited</td>
<td>NR</td>
<td>NR</td>
<td>Cross-sectional</td>
<td>Health clinic attendees (primary care, 7 centres)</td>
<td>NR</td>
<td>6 Months</td>
<td>Need for assistance</td>
<td>Unspecified, Severe</td>
<td></td>
</tr>
<tr>
<td>Ooi 2011</td>
<td>Questionnaire/Recall</td>
<td>Malaysia</td>
<td>170</td>
<td>41.2</td>
<td>8.02 (64.2)</td>
<td>NR</td>
<td>100</td>
<td>NR</td>
<td>Consecutive</td>
<td>Health clinic attendees (primary care, 7 centres)</td>
<td>NR</td>
<td>1 Year</td>
<td>Symptoms</td>
<td>Unspecified</td>
<td></td>
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<tr>
<td>Parsak 2013</td>
<td>Emergency records</td>
<td>USA</td>
<td>5,534</td>
<td>NR</td>
<td>NR</td>
<td>All patients included that met inclusion criteria</td>
<td>NR</td>
<td>NR</td>
<td>Retrospective</td>
<td>Emergency records from one geographical location</td>
<td>NR</td>
<td>6 years</td>
<td>Assistance of emergency services</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Pettersson 2010</td>
<td>Questionnaire/Recall</td>
<td>Sweden</td>
<td>430</td>
<td>61</td>
<td>63 (45.4)</td>
<td>Macrovascular events 50%-30%</td>
<td>NR</td>
<td>69</td>
<td>Consecutive</td>
<td>Health clinic attendees (primary care, multicentre)</td>
<td>NR</td>
<td>6 Months</td>
<td>Level of assistance / interruption to activities</td>
<td>Unspecified, Severe</td>
<td></td>
</tr>
<tr>
<td>Rombopoulos 2013</td>
<td>Questionnaire/Recall</td>
<td>Greece</td>
<td>6,631</td>
<td>55</td>
<td>NR</td>
<td>Community population (defined geographical locations distributed)</td>
<td>NR</td>
<td>NR</td>
<td>Cross-sectional</td>
<td>Community population (defined geographical locations distributed)</td>
<td>NR</td>
<td>3 Months</td>
<td>Laboratory confirmed clinical symptoms</td>
<td>Unspecified, Severe</td>
<td></td>
</tr>
<tr>
<td>Samann 2012</td>
<td>Questionnaire/Recall</td>
<td>Germany</td>
<td>4,481</td>
<td>56</td>
<td>NR</td>
<td>All participants eligible invited</td>
<td>NR</td>
<td>66</td>
<td>Retrospective</td>
<td>Health insurance database</td>
<td>NR</td>
<td>1 Year</td>
<td>Cosa or glucose/glucagon required</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Sarkar 2010</td>
<td>Questionnaire/Recall</td>
<td>USA</td>
<td>14,357</td>
<td>51</td>
<td>7.6 (59.6)</td>
<td>Stratified random</td>
<td>NR</td>
<td>58</td>
<td>Cross-sectional</td>
<td>Health insurance database</td>
<td>NR</td>
<td>1 Year</td>
<td>Passing out or need for assistance</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Schopman 2009</td>
<td>Questionnaire/Recall</td>
<td>UK</td>
<td>110</td>
<td>51.6</td>
<td>NR</td>
<td>Random</td>
<td>Health clinic attendees (secondary care, diabetes clinic, single centre)</td>
<td>Cross-sectional/Prospective</td>
<td>6.5 (median) (insulin)</td>
<td>NR</td>
<td>1 month/1 year</td>
<td>Nedd for assistance or BG &lt;3.3 mmol/L</td>
<td>Severe</td>
<td></td>
<td></td>
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<tr>
<td>Skinner 2013</td>
<td>Questionnaire/Recall</td>
<td>Australia</td>
<td>1,926</td>
<td>NR</td>
<td>NR</td>
<td>Random</td>
<td>Diabetes registry/database (national)</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>1 week</td>
<td>Low BG</td>
<td>Unspecified</td>
<td></td>
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<thead>
<tr>
<th>First author</th>
<th>Data Source</th>
<th>Country</th>
<th>Sample size</th>
<th>Male %</th>
<th>Mean HbA1c%</th>
<th>CVD events</th>
<th>Hypo: No hypo</th>
<th>Non-white %</th>
<th>Mean Age (years)</th>
<th>Sampling method</th>
<th>Sample source</th>
<th>Design</th>
<th>Length of therapy (years)</th>
<th>Time hypo measured over</th>
<th>Hypo definition</th>
<th>Analysisa</th>
</tr>
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<tbody>
<tr>
<td>Stahl 1999</td>
<td>Emergency records</td>
<td>Switzerland</td>
<td>2,529</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Emergency records from one geographical location</td>
<td>Retrospective</td>
<td>NR</td>
<td>1 Year</td>
<td>Hospital Admission</td>
<td>Severeb</td>
<td></td>
</tr>
<tr>
<td>Stargardt 2009</td>
<td>Questionnaire/Recall</td>
<td>Germany</td>
<td>392</td>
<td>57.4</td>
<td>7.2 (55.2)</td>
<td>NR</td>
<td>62.7</td>
<td>56.7</td>
<td>NR</td>
<td>Convenience</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>6 Months</td>
<td>According to level of assistance/ interruption to activities</td>
<td>Unspecified, Mildb, Severeb</td>
<td></td>
</tr>
<tr>
<td>Vekau 2008</td>
<td>Questionnaire/Recall</td>
<td>France</td>
<td>400</td>
<td>53.6</td>
<td>7.2 (55.2)</td>
<td>26%</td>
<td>53%</td>
<td>NR</td>
<td>62.1</td>
<td>Non-random</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>7 Months</td>
<td>According to level of assistance/ interruption to activities</td>
<td>Unspecified, Mildb, Severeb</td>
<td></td>
</tr>
<tr>
<td>Whitmer 2009</td>
<td>Emergency records</td>
<td>USA</td>
<td>16,667</td>
<td>54.6</td>
<td>NR</td>
<td>Heart disease</td>
<td>84%</td>
<td>62%</td>
<td>44% (29%</td>
<td>All participants eligible invited</td>
<td>Diabetes registry/database</td>
<td>Prospective</td>
<td>NR</td>
<td>10.42 years (mean)</td>
<td>Assistance needed to actively administer carbohydrate</td>
<td>Severeb</td>
</tr>
<tr>
<td>Williams 2012</td>
<td>Questionnaire/Claims database</td>
<td>USA</td>
<td>813</td>
<td>58</td>
<td>NR</td>
<td>NR</td>
<td>64.9</td>
<td>56</td>
<td>Random</td>
<td>Health insurance database</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>1 Year</td>
<td>Symptoms or BG &lt; 70mg/dL</td>
<td>Unspecified, Mildb, Severeb</td>
<td></td>
</tr>
<tr>
<td>Yun 2013</td>
<td>Questionnaire/Recall/Emergency dep records</td>
<td>Korea</td>
<td>878</td>
<td>38</td>
<td>8.8 (72.7)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>55.3</td>
<td>Consecutive</td>
<td>Health clinic attendees (outpatients, single centre)</td>
<td>Prospective</td>
<td>NR</td>
<td>10.42 years (median)</td>
<td>Assistance needed to actively administer carbohydrate</td>
<td>Severeb</td>
</tr>
<tr>
<td>The UK Hypoglycaemia study group 2007</td>
<td>Prospective diary</td>
<td>UK</td>
<td>274</td>
<td>70.1</td>
<td>7.5 (58.5)</td>
<td>NR</td>
<td>NR</td>
<td>61</td>
<td>Stratified</td>
<td>Health clinic attendees (secondary diabetes, 6 centres)</td>
<td>Prospective</td>
<td>NR</td>
<td>10.50 months (median)</td>
<td>Symptoms or glucose BG &lt; 3.0 mmol/L + according to level of assistance</td>
<td>Mildb, Severeb</td>
<td></td>
</tr>
<tr>
<td>Zhang 2013</td>
<td>Questionnaire/Recall</td>
<td>China</td>
<td>586</td>
<td>59.2</td>
<td>7.5 (58.5)</td>
<td>100</td>
<td>55.1</td>
<td>Consecutive</td>
<td>Health clinic attendees (secondary care, outpatients, single centre)</td>
<td>Cross-sectional</td>
<td>NR</td>
<td>3 Months</td>
<td>NR</td>
<td>Unspecified</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HbA1c - glycated haemoglobin, NR—not reported, BG—blood sugar, Hypo—hypoglycaemia.

a Mild/moderate hypoglycaemia—no third party assistance was needed

b Severe hypoglycaemia—third party assistance was required.

c Unspecified hypoglycaemia—severity not specified when gathering some or all of the hypoglycaemia data

d Category for meta-analysis

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explanatory factors (43/46, 93.5%). However, under half of studies scored well for sample bias (15/46, 32.6%).

Prevalence of people who have experienced hypoglycaemia

Overall 46 studies involving 532,542 participants were included for the meta-analyses examining the prevalence (proportion of people who had experienced hypoglycaemia). Eight papers involving 4,083 participants, measuring over a period of 1 month to 10.5 months, reported mild/moderate hypoglycaemia. The pooled prevalence of people who had experienced hypoglycaemia was 0.45 (95% CI 0.34 to 0.57; Fig 2). In relation to those on insulin as a diabetes treatment regime, the prevalence was 0.52 (95% CI 0.37 to 0.67) compared with 0.33 (95% CI 0.24 to 0.42) for sulphonylureas. Data were not available to calculate any further treatment categories.

The meta-analysis for the prevalence of severe hypoglycaemia included 40 papers involving 528,310 participants, measuring over a period of 1 month to 22 years, with a pooled prevalence of 0.06 (95% CI 0.05 to 0.07; Fig 3). For people on insulin as a treatment regime, the prevalence...
was relatively higher at 0.21 (95% CI 0.16 to 0.25) when compared with regimens involving sulphonylurea (0.05 [95% CI 0.02 to 0.07]), non sulphonylurea therapies (0.05 [95% CI 0.03 to 0.07] and mixed oral glucose lowering therapies (0.05 [95% CI 0.02 to 0.07]); Table 2). In 14 studies involving 473,481 participants, severe hypoglycaemic episodes were restricted to only

Fig 3. Forest plot showing the proportion of people experiencing severe hypoglycaemia in each study and the overall pooled estimate. Boxes and horizontal lines represent proportion of people experiencing severe hypoglycaemia and 95% CI for each study. Size of box is proportional to weight of that study result. Diamonds represent the 95% CI for pooled estimates of effect and are centred on pooled hypoglycaemia incidence.

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those requiring medical assistance (not any third party assistance), the overall pooled prevalence was 0.05 (95% CI 0.03 to 0.06). When these studies were excluded the overall pooled prevalence for severe hypoglycaemia was 0.08 (95% CI 0.06 to 0.10), see Table 2.

Eighteen papers involving 24,804 participants, measuring over 1 month to 1 year, reported data for the prevalence of unspecified type of hypoglycaemia (severity of hypoglycaemia does not vary between studies). The prevalence and incidence of hypoglycaemia by severity and treatment regime are presented in Table 2.

### Table 2. Proportion of people experiencing hypoglycaemia and the number of episodes per patient-year by severity and treatment regime.

<table>
<thead>
<tr>
<th>Treatment Regime</th>
<th>Unspecified</th>
<th>Mild/Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion</td>
<td>Rate</td>
<td>Proportion</td>
</tr>
<tr>
<td>Insulin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (2539)</td>
<td>3 (649)</td>
<td>5 (728)</td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>0.57 (0.42 to 0.71)</td>
<td>0.52 (0.37 to 0.67)</td>
<td>0.21 (0.16 to 0.25)</td>
</tr>
<tr>
<td>I²</td>
<td>98.4%</td>
<td>94.5%</td>
<td>99.7%</td>
</tr>
<tr>
<td>Sulphonylureas&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (8390)</td>
<td>2 (508)</td>
<td>8 (12872)</td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>0.26 (0.02 to 0.50)</td>
<td>Insufficient data</td>
<td>0.05 (0.02 to 0.07)</td>
</tr>
<tr>
<td>I²</td>
<td>98.4%</td>
<td>69.1%</td>
<td>98.5%</td>
</tr>
<tr>
<td>Non-sulphonylureas&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4 (2135)</td>
<td>0 (0)</td>
<td>2 (646)</td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>0.26 (0.02, to 0.50)</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>I²</td>
<td>99.6%</td>
<td>Insufficient data</td>
<td></td>
</tr>
<tr>
<td>Mixed oral-glucose lowering therapies&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2 (568)</td>
<td>0 (0)</td>
<td>7 (35041)</td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>0.40 (0.30 to 0.51)</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>I²</td>
<td>0.0%</td>
<td>99.5%</td>
<td></td>
</tr>
<tr>
<td>Proportion overall&lt;sup&gt;e&lt;/sup&gt;</td>
<td>18 (24804)</td>
<td>5 (5575)</td>
<td>8 (4083)</td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>0.43 (0.36 to 0.50)</td>
<td>0.45 (0.34 to 0.57)</td>
<td>0.06 (0.05 to 0.07)</td>
</tr>
<tr>
<td>I²</td>
<td>99.4%</td>
<td>97.8%</td>
<td>99.7%</td>
</tr>
</tbody>
</table>

Abbreviations: CI, Confidence Interval.

<sup>a</sup> Insulin (with or without oral-glucose lowering therapies)

<sup>b</sup> Sulphonylureas (non-insulin but with or without other oral-glucose lowering therapies)

<sup>c</sup> Non-sulphonylureas (non-insulin and non-sulphonylurea oral-glucose lowering therapies)

<sup>d</sup> Mixed oral-glucose lowering therapies (non-insulin but no further description given relating to type of oral-glucose lowering therapies).

<sup>e</sup> All studies combined regardless of treatment

DOI:10.1371/journal.pone.0126427.002
experienced was not specified when data collecting, assumed to cover both mild/moderate and severe episodes), with a pooled prevalence of 0.43 (95% CI 0.36 to 0.50).

There was high heterogeneity shown between studies reporting mild/moderate (I² = 98.0%), severe (I² = 99.7%) unspecified (I² = 99.4%) hypoglycaemia prevalence. A possible explanatory variable for this was the different time periods hypoglycaemia was measured over between studies. This along with other explanatory variables: year of publication, mean HbA1c, mean age, and percentage of male participants were carried out in a meta-regression on the prevalence of, mild/moderate, severe and unspecified hypoglycaemia. No variables were shown to be statistically significant, see Table 3.

Incidence of hypoglycaemic episodes per person-year

The pooled incidence of hypoglycaemic episodes per person-year for mild/moderate and severe hypoglycaemia was 19.03 (95% CI 0.00 to 51.08) and 0.80 (95% CI 0.00 to 2.15, Table 2), respectively. Unspecified hypoglycaemia episodes showed a pooled incidence of 27.78 (95% CI 0.00 to 58.20; per person-year). Those on insulin experienced 23.31 (95% CI 0.00 to 58.98) mild/moderate and 1.05 (95% CI 0.00 to 3.69) severe episodes per person-year. Data were not available to calculate any further treatment categories for mild/moderate, but a further incidence of 0.01 (95% CI 0.00 to 0.55) for those on sulphonylureas experiencing severe episodes was estimated.

Publication bias

There appeared to be publication bias for studies reporting prevalence of severe hypoglycaemia (p = 0.04), with studies reporting lower prevalence appearing to be missing from published literature (funnel plot can be found in S2 Fig). However, when analysis was carried out separating
the study results relating to medical assistance only, from any third party assistance, there was no evidence of publication bias (p = 0.41 and; p = 0.36 respectively). No other significant publication bias was shown for prevalence (mild/moderate p = 0.09, unspecified p = 0.37) or for incidence (mild/moderate p = 0.06, severe p = 0.91, unspecified p = 0.06).

Discussion

This review of 46 studies (n = 532,542) estimates that the prevalence (proportion of people) of hypoglycaemia is 45% for mild/moderate and 6% for severe in population-based studies of type 2 diabetes, and that on average an individual with T2DM experiences 19 mild/moderate episodes and 0.8 severe episodes per year. Hypoglycaemia is particularly prevalent amongst those on insulin (mild/moderate: prevalence = 52%, incidence = 23 events/year; severe: prevalence = 21%, incidence = 1 event/year, yet still fairly common for treatment regimens that include sulphonylureas (mild/moderate: prevalence = 33%, incidence = 1.92 events/year; severe: prevalence = 5, incidence = 0.01 events/year. Severe hypoglycaemia prevalence was the same 5% for those on treatment regimens that did or did not include sulphonylureas.

Relationship to other literature

Previous literature focusing on hypoglycaemia in type 2 diabetes in a real-world setting is limited. One report of severe hypoglycaemia prevalence in clinical trials also considered severe hypoglycaemia prevalence in population based studies, but did not examine mild/moderate episodes nor provide pooled estimates [3]. Various systematic reviews have considered hypoglycaemia prevalence within randomised controlled trials involving people with type 2 diabetes [25–28]. These tend to focus on individuals using insulin and their results indicate that severe hypoglycaemia prevalence is below 1%, which is substantially lower than our pooled estimate of 6% from population-based studies. Mild/moderate hypoglycaemia is reported less in clinical trials, though recent meta-analyses of clinical trials showed pooled prevalences of 10% (range 0.7%- 22%) for those on sulphonylureas [34], and 20% to 52% for those on insulin [35–37]. Our estimate for sulphonylureas was higher at 33% (range 30%- 39%), but for insulin was similar, albeit at the higher end of the scale, at 52% (range 20%- 72%). Mild/moderate hypoglycaemia prevalence was fairly consistent across trials, as was the case in the population-based studies in this review. Randomised controlled trials often do not reflect real life situations as treatment regimens are more aggressively titrated than in standard clinical practice, and participants are often highly selected and generally do not include those at higher risk of hypoglycaemia. Therefore, the generalizability of results from trials is limited.

Strengths and Limitations

To our knowledge, this is the first systematic review and meta-analysis published which focuses on population-based studies of hypoglycaemia in people with type 2 diabetes. The review adhered to the Cochrane recommended standards for systematic reviews [32], involved robust methodology such as duplicate reviewing, and only included population-based studies which reported prevalence and/or incidence rates specifically for a type 2 diabetes population, making the results applicable to the type 2 diabetes general population. The results follow the American Diabetes Association Workgroups recommendations that both the proportion of patients experiencing hypoglycaemia and event rates for each severity are reported [38].

There was high heterogeneity between studies, which was not explained by any of the study level covariates considered. Therefore, the high heterogeneity is likely to be due to the very narrow confidence intervals associated with the proportion estimates, or to other study characteristics which were not measured, reported or extracted. Publication bias appeared to be a
possibility for the published studies on severe hypoglycaemia. However, this appeared to be due to the different definitions of severe hypoglycaemia, since no such bias was present when studies that defined severe as requiring medical assistance were separated from those using the standard definition (requiring any third party assistance).

A strict consensus definition was not found across studies (Table 2). Due to the nature of a large proportion of the studies (questionnaire/interview/medical records), a biochemical definition was rarely used. It must be acknowledged that this does create some difficulty when collating and combining results across studies. For some studies this may have caused under or over reporting. Subsequently, the only way to define and analyse hypoglycaemia was by severity and whether or not third party assistance was required during an episode.

The way in which studies categorised different glucose lowering therapies also varied considerably, if indeed they reported hypoglycaemia by treatment categories at all. Therefore, it was only possible to use broader treatment categories in these analyses. It is important to note here also, that the event rate calculated for severe hypoglycaemia in those using sulphonylureas may appear particularly low. This is likely to be due to two of the three studies used to calculate this result only measuring “very severe” hypoglycaemia, those that specifically needed emergency treatment.

Additionally, studies varied considerably in length of time hypoglycaemia prevalence was related to; as a result a specific time period for prevalence could not be established. This was particularly the case for severe hypoglycaemia. However, a meta-regression was carried out for time hypoglycaemia was measured over on prevalence and it was not found to significantly affect the prevalence reported between studies.

Data from some studies could not be grouped by the severity of hypoglycaemia (mild/moderate or severe). These data were therefore labelled as “unspecified” and assumed to include any type of hypoglycaemic episodes. Nocturnal hypoglycaemia was not analysed due to the lack of reporting within studies.

Implications for practice

This review shows that hypoglycaemia is considerably prevalent amongst people with type 2 diabetes. We estimated that an individual with type 2 diabetes experiences one severe episode of hypoglycaemia per year on average. Severe episodes are a burden on both the individual and healthcare utilisation, due to their cost and the significant dangers that can result from an episode [1, 3]. The estimate of 19 mild/moderate episodes on average per year is also important. This quantity of mild/moderate episodes could substantially impact on work, social life and driving, as well as potentially decreasing general quality of life and increasing risk of severe events if left untreated [39, 40].

Our results highlight an urgent need for raising awareness within everyday clinical practice, particularly as prior evidence has suggested underreporting within this setting [41]. When considering treatment options, hypoglycaemia risk consideration should be incorporated through the individualisation of treatment regimens prescribed [9]. Blood glucose targets should also be individualised and in some cases a higher target may be optimal for the patient [42].

Educational programmes should be focused on successfully increasing knowledge of hypoglycaemia in relation to appropriate self-treatment methods, risk factors and predisposing symptoms [43], as this has previously been shown to be low in the type 2 diabetes population [44, 45].

Future directions

Research into mild episodes is more challenging than severe episodes in terms of reliability and access to data, with data collection methods limited to constant glucose monitoring,
prospective diary recording, and retrospective recall. Constant glucose monitoring is the most reliable, but can be costly and so generally involve small populations and short data collection periods[46, 47]. Retrospective recall is convenient and least costly, though potentially less reliable.

In some studies (6/46, 13%) severity of hypoglycaemia was not specified when data were collected, and hypoglycaemia definitions also varied across studies (Tables 1 and 2). This could have led to errors in reporting, including participants interpreting the meaning of hypoglycaemia differently, with some perhaps only reporting severe episodes. Therefore, it is important that a standardised definition such as the widely used American Diabetes Association workgroup's[38] is utilised across studies of hypoglycaemia.

More research is needed in relation to potential risks associated with particular glucose lowering therapies. Studies were inconsistent in how they reported treatment regimens, making it difficult to collate data. There is a lack of published population-based literature comparing sulphonylurea and non-sulphonylurea treatment regimens, including the newer glucose lowering therapies.

Conclusion
To our knowledge, this is the first systematic review and meta-analysis of the prevalence and incidence rates of hypoglycaemic events in population-based studies of people with type 2 diabetes. Hypoglycaemia is particularly prevalent amongst those on insulin, yet still fairly common for treatment regimens that do and do not include sulphonylureas. This highlights the subsequent need for educational interventions and individualisation of therapies to reduce the risk of hypoglycaemia. The current evidence also suggests that hypoglycaemia prevalence within clinical trials is likely to be an underestimate.

Supporting Information
S1 Fig. Search strategy for Ovid MEDLINE.
(PDF)
S2 Fig. Funnel plot of population based studies reporting severe hypoglycaemia prevalence in type 2 diabetes.
(PDF)
S1 Table. Quality assessment results table.
(PDF)

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Author Contributions
Conceived and designed the experiments: KK MJD CE AJD. Performed the experiments: CE TR AJD KK. Analyzed the data: CE DB LJG. Wrote the paper: CE AJD KK MJD TR DB LJG. Conducted the meta-analyses and meta-regression: CE. Made the final decisions regarding inclusion/exclusion of all papers: KK. Developed the search strategy, designed the data extraction
and quality assessment tools: CE AJD. Conceived the idea for the review and is guarantor of the overall content: KK MJD. Selected and retrieved relevant papers, carried out extraction/checking of data and quality assessments: CE TR. Provided statistical support for conducting the meta-analyses and meta-regression with statistical support: DB LJG.

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