Prevalence of Impaired Glucose Regulation in Europe: A meta-analysis.

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Abstract

Background: Impaired glucose regulation represents an opportunity to prevent Type 2 diabetes mellitus. It is important to have a clear understanding of the prevalence of this condition in order to be able to plan interventions and health care provision. This paper presents a meta-analysis of literature assessing the prevalence of impaired glucose regulation in the general population of developed countries in Europe.

Methods: Five electronic databases were systematically searched in March 2014 to identify English language articles with general population samples aged 18 and over from developed countries in Europe. Values for the measures of interest were combined using a random effects model and analysis of the effects of moderator variables was carried out.

Results: A total of 5594 abstracts were screened, with 46 studies included in the review. Overall prevalence of impaired glucose regulation was 22.3%. Mean prevalence of impaired glucose tolerance was 11.4% (10.1-12.8) and did not differ by gender. Sample age, diagnostic criteria and country were found to have a significant univariate effect on prevalence of impaired glucose tolerance but only diagnostic criteria remained significant in multivariate analysis. Mean prevalence of impaired fasting glucose was significantly higher in men at 10.1% (7.9-12.7) compared to 5.9% in women (4-8.7). The only moderator variable with a significant effect on impaired fasting glucose prevalence was country.

Conclusions: This meta-analysis shows a moderate prevalence of impaired glucose regulation in developed Europe with over one in five people meeting the criteria for either impaired glucose tolerance, impaired fasting glucose, or both.

Keywords: Prediabetic state; Prevalence; Europe; Meta-analysis.

Introduction

People with Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) have blood glucose levels that are higher than normal but do not meet the diagnostic criteria for Type 2 diabetes mellitus (Type 2 DM). These two states, known collectively as Impaired Glucose Regulation (IGR), confer an increased risk of developing type 2 DM [1]. IGT was first formally recognised in published diagnostic guidance for diabetes in 1979 [2] while IFG was not recognised until 1997 [3] with the precise glucose levels used to diagnose IFG and IGT depending upon the specific guidance used. In the most current guidance from ADA [4] and WHO [5], IGT is defined as an elevated two hour plasma glucose (2hPG) concentration after an oral glucose tolerance test (OGTT) of between 7.8 and 11.1 mmol/l and a fasting plasma glucose (FPG) concentration of less than 7 mmol/l. The ADA define IFG as an FPG of between 5.6 and 6.9mmol/l and WHO define it as an FPG of between 6.1 to 6.9 mmol/l and (if measured) a 2hPG in the normal range (less than 7.8mmol/l).

Although people with IGR are at an increased risk of type 2 DM, research has shown that by making lifestyle changes they can prevent or delay progression to type 2 DM [1]. With prevalence of type 2 DM increasing rapidly, a diagnosis of IGR represents an opportunity for intervention to reduce the burden of type 2 DM [6]. It is important to have a full and clear understanding of the prevalence of this condition in order to be able to plan such interventions and health care provision. Estimates of IGR prevalence vary greatly from study to study. A study of IGR prevalence in 13 population groups in 9 European countries reported estimates of IGR ranging from 3.2% to 64.2% [7]. It is likely that this variation in reported rates is due to a number of factors such as distribution of age and sex in the sample, differences in the data collection methodology and in the criteria used to classify IFG and IGT. In order to provide a clearer understanding of IGR prevalence and the factors affecting reported estimates, we carried out a meta-analysis of observational studies assessing the prevalence or incidence of IGR in the general population of adults in developed countries in Europe. We determined an overall prevalence estimate for IGR and examined moderator variables that potentially influenced this estimate.

Methods

Literature search and study selection

A meta-analysis of published studies reporting prevalence and incidence of IGR was undertaken in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reviews [8]. All authors have previously conducted systematic reviews that have been published in peer reviewed journals. After consulting colleagues with expertise in meta-analysis and a librarian at the University of Stirling regarding the search strategy, a search was conducted in MEDLINE, EMBASE, CINAHL, Health Source and PsycInfo for articles published in English from January 1948 to March 2014. The following combination of search terms were used with each database: (prevalence or incidence) and (impaired glucose tolerance or impaired fasting glucose or prediabetes or pre-diabetes or impaired glucose regulation). Key authors and experts in the in the field were not contacted due to the time consuming nature of this process with no guarantee of obtaining relevant information.

After removing duplicates, the title and abstract of each paper were screened by two authors (CE and JE or EF) against the following inclusion criteria:

1) Population: general population, men or women, aged 18 and over, living in a developed country in Europe (as defined by the Financial Times Stock Exchange).

2) Outcome measure: prevalence of IFG and/or IGT diagnosed using FPG and/or 2hPG in a way that is consistent with WHO criteria published from 1980 to 2006 or National Diabetes Group/ADA criteria from 1979 to 2011.

3) Study design: observational study, published in English.

All papers were screened by CE; JE and EF each screened half of the papers. In cases of disagreement between authors about the inclusion of a paper, the full text of the paper was accessed and consensus was reached through discussion. The review was limited to developed countries in Europe because of the wide differences in prevalence of type 2 DM and impaired glucose regulation between developed

and developing countries [9, 10]. This removed one potential source of heterogeneity in the review and also ensured that it is relevant for informing care and development of interventions in the context of developed health care systems. Studies were defined as having a sample drawn from the general population if it was drawn from a source that covered the majority of the population, such as census, other population register or general practice register (in countries where registration at general practice is near to universal). If this information was not reported, studies were only included if the paper explicitly stated that the sample was drawn from a general population. Studies that selected people who were at high risk of IGR (due to family history of type 2 DM, or lifestyle and medical factors), or who were recruited from hospital clinics or workplaces, were excluded. The full text of papers were retrieved for studies that were considered relevant, but also for those that contained insufficient information to allow judgement of relevance. Reference lists of included articles were reviewed to identify any additional relevant articles.

Data extraction and coding

Data were extracted and summarised from potentially relevant studies by one author (CE) using a standardised data extraction form based on the example provided by the Centre for Reviews and Dissemination [11]. Confidence intervals were calculated where possible for studies that did not report these for prevalence figures. Where there were multiple papers published that were based upon the same sample, only the paper reporting the most complete and definitive results was included. However, more than one paper from the same sample was included in the review if each paper reported on a unique aspect of the findings.

The following information was extracted from each included study: first author, journal name and year of publication, country of study population, study period, study sample type, study design, age range, response rate, sample size, gender distribution in the sample (100% male, 100% female or mixed) and diagnostic criteria for IGT and/or IFG. The outcome measures extracted were number and proportion of sample with IGT and/or IFG, and number and proportion of sample with IGT and/or IFG by age and gender. The diagnostic criteria for IGT were split into four categories, with the widest criteria in Category 1 through to the narrowest in Category 4: 1) 2hPG 7.8-<11.1mmol/l (e.g. ADA

1997 [3]); 2) FPG <8.0mmol/l and 2hPG 8.0-<11.0mmol/l (e.g. WHO 1980 [12]);]); 3) FPG<7.8mmol/l and 2h 7.8-<11.1mmol/l (WHO 1985 [13]) 4) FPG <7.0mmol/l and 2hPG 7.8-<11.1mmol/l (e.g. WHO 2006 [5]). Similarly, diagnostic criteria for IFG were split into three categories, with the widest criteria in Category 1 through to the narrowest in Category 3: 1) FPG 5.6-6.9mmol/l (e.g. ADA 2003 [14]); 2) FPG 6.1-6.9mmo/l (e.g. ADA 1997 [3]); 3) FPG 6.1-6.9 and 2hPG <7.8mmo/l (WHO 1999 [15])

Where studies reported multiple prevalence estimates according to different diagnostic criteria, only one prevalence estimate was included in the meta-analysis to avoid dependency effects. For both IGT and IFG, the prevalence estimate generated by the most definitive criteria was selected, i.e. defined using both fasting and 2 hour samples. Otherwise, the criteria that was most commonly used in the papers included in the review was selected so that the estimate would be most comparable to other studies in the review. For studies reporting multiple prevalence estimates by other factors, such as age or year, an average of the estimates was calculated and used in the analysis.

Quality appraisal

The quality of included studies was assessed using a checklist based upon the example published by the Joanna Briggs Institute [16] which was designed for assessment of quality in systematic reviews of prevalence and incidence. Quality assessment was completed for all included papers by one author (CE) and a list of all identified weaknesses was compiled. The list was then discussed by all of the authors and the weaknesses were categorised as either major or minor. Major weaknesses were those that put the study at high risk of bias or made the risk of bias difficult to assess. They included not reporting participation rate, very low participation rate (<50%) or not reporting the source of the study sample (e.g. census, general practice register). Participation rates can be defined in many ways but for this review the participation rate (recoded during data extraction if necessary and possible) was the proportion of eligible people sampled who completed testing for IGT or IFG. Minor weaknesses were those that were less likely to put the study at risk of bias, and included low participation rate (50-70%), not reporting differences between participants and non-participants, not reporting who carried

out blood samples, not reporting the proportions of men and women in the sample, and not reporting the details of fasting duration or what happened to non-fasters.

Included studies were then given a quality rating as follows:

1: Only minor weaknesses, excluding a low participation rate.

2: Only minor weaknesses, including a low participation rate.

3: One major weakness.

Data Analysis

The meta-analysis was carried out using the Comprehensive Meta-Analysis software version 3.3.070 (Biostat, Englewood, NJ). For each study, the proportion of people with IGR was transformed into a logit event rate effect size and the standard error associated with this was calculated [17]. The logits were retransformed to proportions after analysis to aid interpretation of the results. Combined effect sizes were calculated and analyses were carried out both including and excluding outlying logit event rates. No significant differences were found so outliers were retained in the analyses.

Significance tests and moderator analysis were carried out using a random effects model. Fixed effects models make the assumption that the effect size observed in a study estimates the corresponding population effect with random error that comes only from the chance factors associated with subject level sampling error [17]. In contrast, random effects models allow for the possibility that there are also random difference between studies that are not only due to sampling error but as a result of some other factor such as variations in procedures, measures or settings. The choice of the random effects model to combine studies in this meta-analysis was based upon literature on IGR prevalence which suggests that the variability in reported prevalence for IGR may be the result of the use of different methodologies and criteria [7].

The homogeneity of studies was evaluated using the Q test where the null hypothesis states that variability of the effect sizes is the result of sampling error only. If the assumption of homogeneity is

violated it is customary for sources of variation to be explored by studying moderator variables. Q and I^2 statistics were also calculated to assess differences in combined effect sizes for sets of studies grouped according to moderator variables.

Categorical moderator variables were analysed using an analysis of variance for meta-analysis. Differences between subgroups of these variables were explored using a test of interaction. The between study homogeneity statistic (Q_B) reflects the amount of heterogeneity that can be attributed to the moderator variable. The within study homogeneity statistic indicates the degree of heterogeneity that remains in the category in question (Q_W) and the I^2 statistic shows the proportion of the variation that is due to heterogeneity rather than sampling error. For continuous variables, a simple weighted regression was used, where Q_R represents the proportion of variability associated with the regression model and Q_E indicates the variability unaccounted for by the model.

Results

Description of Included Studies

Figure 1 shows a PRISMA flow diagram of studies identified by the search. The search identified 5,594 abstracts of which 148 were potentially relevant after title and abstract screening. The full text articles were retrieved and assessed against the inclusion criteria, resulting in 46 included studies reported in 53 papers (additional papers: [18-24]). These 46 studies included a total of 77,379 participants. The characteristics of the studies included in the review are presented in Table 1 (online supplementary file). Of the 46 studies included, 13 assessed prevalence of IGT [25-37], 11 assessed the prevalence of IFG [38-48] and 22 reported the prevalence of both IFG and IGT [49-70]. In total, prevalence of IGT was reported in 35 different samples and IFG in 33 samples No studies were identified that assessed incidence of IGR. Of the 35 studies where IGT prevalence was reported, prevalence was reported separately for men and women in 19. For IFG, 25 out of 33 studies reported prevalence separately by sex. Studies were conducted across 11 of the 17 countries defined as developed European countries: Spain (n=11), UK (n=9), Finland (n=8), Sweden (n=5), Italy (n=4), France (n=3), Germany (n=2), Portugal (n=1), Denmark (n=1), the Netherlands (n=1) and Greece (n=1). No additional papers were identified by manual searching of reference lists.

Quality of Studies

The quality category assigned to each study is reported in Table 1. Six studies were identified that had two major weaknesses [71-76]: all six had not reported from where participants were selected, and also had either a low or unspecified participation rate. These studies were excluded from the review as this particular combination of problems made it difficult to assess the risk of bias in the study. Another study was excluded from the review as the reported prevalence estimates, sample size and the number with IGT reported in the paper were inconsistent with each other [77]. The majority of included studies were classed as either the higher (n=15) or middle quality category (n=16) and therefore had only minor weaknesses. The remaining studies fell in to the lower quality category (n=16) and in addition to any minor weaknesses also had one major weakness. The most common major weaknesses found in the lower quality studies were a very low participation rate (n=5) followed

by non-reporting of where participants were selected from (n=8) and non-reporting of participation rate (n=2). Of the weaknesses categorised as minor by the authors of this meta-analysis, the most common problems were non-reporting of who carried out blood glucose measurements (n=32), non-reporting of checks on fasting status of participants (n=32); non-reporting of information on non-responders (n=26) and low participation rate (n=18). Less common minor problems were non-reporting of details about the duration of fasting prior to measuring blood glucose (n=8) and non-reporting of the sex split of the sample (n=6).

Analysis of Outliers

In total four outliers were identified, three for IGT [31, 35, 36] and one for IFG [50]. The three outliers for IGT all reported prevalence of over 28% and the outlier for IFG reported prevalence in females of 17.6%. Sample age would appear to be the most obvious explanation for the high prevalence estimates in these studies, with three having samples aged 60 and older [31, 36, 50] and one with a sample aged 55 [35].

Mean Prevalence of IGT

The mean prevalence of IGT overall was 11.4% (95% CI: 10.1-12.8). The mean prevalence of IGT in men was 12.9% (10-16.4), 13.2% in women (10.5-16.5) and 9.9% (8.3-11.7) in mixed samples. There was no significant difference in prevalence of IGT between men and women ($Q_{(1)}$=0.02; p=0.089). The analysis of homogeneity in the data with regards to sex showed variability within the studies assessing prevalence in men ($Q_{(19)}$=500.73; p<0.001), those with women ($Q_{(19)}$=670.22; p<0.001) and those with mixed samples ($Q_{(12)}$=293.58; p<0.001).

Analysis of Moderators for IGT

As there was no significant difference in prevalence of IGT by sex, the analysis of prevalence by moderator variables is presented in overall terms. Table 2 shows the individual effects of different categorical moderator variables with the unit of analysis in all cases being the study. The effect of the continuous variable year is presented separately below. Sample age, diagnostic criteria and country the study was conducted in were found to have a significant effect on prevalence of IGT whereas the quality category of the study and year of data collection did not.

Sample Age

The highest prevalence was found in samples aged 66 and over (25.1%; 17.8-34.1) followed by samples aged 30 to 65 (11.8%; 9.8-14.2) and the lowest prevalence was in samples aged 18 and over (9.4%; 7.1-12.4).

Diagnostic Criteria

Analysis of the effect of the four diagnostic categories on IGT prevalence found the highest prevalence estimate in studies using the second widest diagnostic criteria (19.7%; 13.9-27.2). Contrary to what would be expected, the lowest prevalence estimate of 7.4% (5.7-9.6) was found in studies using the widest category. However, this category contained only two studies so the results need to be interpreted with caution. The next lowest prevalence was found for studies using the second narrowest criteria (10.3%; 8.6-12.2). The widest category had a mean prevalence of 13% (9.2-18.2), but again this category contained only two studies so results should be interpreted with caution.

Country

In the analysis by country, the highest prevalence was found in studies conducted in Finland (19.9%; 14.8-26.2) and the lowest in Italy (6.9%; 5.4-8.7).

Year

With regard to the year in which data collection was completed, the simple regression for meta-analysis revealed no relationship between this variable and prevalence rates for IGT ($Q_{R(1)}$=2.8, R^2=4%, p=0.0942).

Multivariate analysis

With the complexity of the univariate results and the fact that none of the moderator variables alone can explain a substantial part of the observed variability in prevalence of IGT, a weighted multiple regression was performed in order to explore which variables independently made the greatest contribution to the variability in prevalence of IGT. Variables that were significant in the univariate analyses (sample age, diagnostic criteria and country) were entered in to the model. These three variables accounted for 35% of total observed variability ($Q_{R(13)}$=39.88, p<0.001, see Table 3 for full results) but only diagnostic criteria remained statistically significant when the other two variables were held constant. However, the residual model was also statistically significant ($Q_{E(17)}$=475.54;

$p<0.001$, $I^2=96.4\%$) meaning that there was still variability in the data that was not explained by the variables analysed.

Mean Prevalence of IFG

The mean overall prevalence of IFG was 8.4% (7.1-9.9). The mean prevalence of IFG in males was 10.1% (7.9-12.7), 5.9% in females (4-8.7) and 8.1% (6.1-10.6) in mixed samples. The prevalence of IFG was significantly higher in men than women ($Q_{(1)}=5.28$; $p=0.022$). The analysis of homogeneity in the data with regards to sex showed variability within the studies with men ($Q_{(14)}=495.35$; $p<0.001$), those with women ($Q_{(13)}=747.51$; $p<0.001$) and those with mixed samples ($Q_{(17)}=1179.74$; $p<0.001$).

Analysis of Moderators for IFG

As significant differences in IFG prevalence existed between men and women, analyses were conducted and presented separately by gender. Table 4 shows the individual effects of different categorical moderator variables. The effect of the continuous variable year is presented separately below. The country in which the study was conducted had a significant effect on prevalence for both men and women. Sample age, quality category, diagnostic criteria and year had no effect on prevalence in either men or women.

Country

For both men and women prevalence was highest in Greece (men: 20.5%, 18.5-22.6; women 12%, 10.5-13.7) and lowest in Germany (men: 4.2%, 3.1-5.7; women: 1.9%, 1.1-3.2). However, there was only one study conducted in each of these countries so results must be interpreted with caution.

Year

With regard to the year in which data collection was completed, the simple regression for meta-analysis revealed no relationship between this variable and prevalence rates for IFG in men ($Q_{R(1)}=0.75$, $R^2=0\%$, $p=0.385$) or women ($Q_{R(1)}=0.07$, $R^2=0\%$, $p=0.785$).

Mean Prevalence of combined IGT and IFG

The term 'combined IGT and IFG' is used to refer to individuals who meet the criteria for both IGT and IFG. The prevalence of combined IGT and IFG was reported in 11 studies included in the review. The mean overall prevalence of combined IGT and IFG was 2.5% (2-3.2). The mean prevalence in men was 2.7% (1.1-6.5), 1.3% in women (0.3-4.8) and 2.6% (2-3.3) in mixed samples. There was no significant difference in combined prevalence of combined IGT and IFG between men than women ($Q_{(1)}$=0.85; p=0.356). The analysis of homogeneity in the data with regards to sex showed variability within the studies with men ($Q_{(1)}$=8.78; p=0.003), those with women ($Q_{(1)}$=7.09; p=0.008) and those with mixed samples ($Q_{(8)}$=68.7; p<0.001).

Analysis of Moderators for combined IGT and IFG

As there was no significant difference in prevalence of combined IGT/IFG by sex, the analysis of prevalence by moderator variables is presented in overall terms. Table 5 shows the individual effects of different moderator variables with the unit of analysis in all cases being the study. All studies assessing combined IGT and IFG used the same diagnostic criteria so this moderator variable is not included in the analysis. Sample age and country in which the study was conducted were found to have a significant effect on prevalence of IGT whereas the quality category of the study did not.

Sample Age

The highest prevalence was found in samples aged 18 and over (3.5%; 2.5-4.7) and the lowest prevalence was in samples aged 30 to 65 (1.9%; 1.5-2.5).

Country

In the analysis by country, the highest prevalence was found in studies conducted in Spain (3.4%; 2.5-4.7) and the lowest was in Germany (1.2%; 0.8-1.9). However, there was only one study conducted in Germany so results must be interpreted with caution.

Year

With regard to the year in which data collection was completed, the simple regression for meta-analysis revealed no relationship between this variable and prevalence rates for combined IGT and IFG ($Q_{R(1)}$=0.1, R^2=0%, p=0.751).

Mulivariate analysis

A weighted multiple regression was performed in order to explore which variables made the greatest contribution to the variability in prevalence of combined IGT and IFG. Variables that were significant in the univariate analyses (sample age and country) were entered in to the model. These three variables accounted for 47% of total observed variability ($Q_{R(7)}$=14.92, p=0.037, see Table 6 in online supplementary material for full results) but neither variable accounted for a significant amount of variance alone when the other variable was held constant. However, the residual model was also statistically significant ($Q_{E(3)}$=15.46; p<0.001) meaning that there was still variability in the data that was not explained by the variables analysed.

Discussion

This meta-analysis of 77,379 participants in 46 studies reported mean prevalence estimates of 11.4% for IGT, 8.4% for IFG and 2.5% for combined IGT and IFG. This suggests that the overall prevalence of IGR could be as high as 22.3%. No differences were found for prevalence of IGT or combined IGT and IFG by gender, but IFG estimates were found to be significantly higher in men than women. An increase in prevalence of IGT was found with increasing sample age. Diagnostic criteria and country were also found to have an effect on IGT prevalence. The only variables that had a significant effect on IFG prevalence was the country in which the study was conducted. There were no clear trends in either IGT or IFG prevalence over time.

The study methods were systematic and robust. We used independent reviewers to screen all of the titles and abstracts identified by the search for inclusion in the review. All decisions on the inclusion of papers were discussed and agreed upon by all three authors. A thorough quality assessment was conducted for all studies considered for inclusion using a template designed for observational epidemiology studies and the majority of studies included were of high quality. The methodology had only minor limitations: only papers published in the English language were included, experts in the field were not contacted, grey literature was not identified and data extraction was only carried out by one author.

The quality assessment ensured that the majority of studies included in the review had relatively good participation rates and recruited participants from sources that have coverage of the majority of the population (e.g. census) using appropriate methods (e.g. random sample or whole population). This allows us to be reasonably confident that the included studies used samples that were representative of the general population. Indeed, quality category of the study was not found to have any significant effect on prevalence of IGR. Although participation rates were generally good for the majority of included studies, around one third of studies had participation rates that would be classified as average at between 50 and 70%, and one tenth of studies had very low participation rates of less than 50%. Non-reporting of various methodological details was a common problem which made it difficult to assess fully the quality of some studies. However, the impact of this problem on the quality of the

review was minimised by the decision to exclude any studies that had more than one weakness defined by the authors as major. Collating data on IGT and IFG prevalence was also made difficult by heterogeneity in approaches to sampling, methods used to collect blood samples and the criteria used to define IFG and IGT. This heterogeneity may have accounted for some of the inconsistencies in findings.

It is generally accepted that around 15% of adults in developed countries have some type of IGR, even though empirical estimates of prevalence vary widely [78]. This figure of 15% is based upon WHO criteria and comes from studies conducted in Europe, Asia and the United States, whereas our estimates are based on both WHO and recent ADA criteria which have a wider range of values for the diagnosis of IFG. Consistent with other research in Europe and the United States, we found that prevalence of IGR increased when wider criteria were used, although these findings were not statistically significant for IFG [16]. It is possible that our inclusion of studies using the new ADA criteria may have inflated the IGR estimate. However, the impact is unlikely to be large as the majority of included studies are based upon older, narrower criteria for IGR. Given the differences between our review and the studies upon which the 15% estimate was based, these estimates therefore accord well with each other.

The trends found in this review of higher prevalence of IFG in men compared to women, higher prevalence of IGT but not IFG with increasing age and the higher prevalence of IGT compared to IFG are all consistent with the findings of the DECODE study in Europe and the DECODA study in Asia that explored these factors in 10 and 13 different samples respectively [7, 79-81]. However, we found no difference in IGT prevalence between men and women, whereas the DECODE and DECODA studies reported higher IGT prevalence in men compared to women; although it has been noted that these sex differences were only significant in specific age groups and were less robust than those found for IFG.

With IGR existing on a continuum with type 2 DM and sharing the same risk factors, we would expect to see increases in IGR over time mirroring those seen for type 2 diabetes [82]. One study

included in this paper that assessed four different samples recruited in the same way at four time points did find significant increases in both IGT and IFG between 1990 and 2004 [55]. However, the various factors identified by this review that influence IGR prevalence, such as age, gender and diagnostic criteria, and the differences in methodologies found across included studies, may have masked any possible temporal trends.

In summary, this is the first meta-analysis to bring together all the relevant evidence relating to IGR prevalence in Europe and to make sense of disparate findings. In the general population of developed Europe, around 1 in 5 people meet the criteria for either impaired glucose tolerance, impaired fasting glucose, or both. These figures provide a basis for the planning of interventions and health care provision for the prevention of type 2 DM. We now recommend that similar meta-analyses be conducted in other populations for comparison, for example those from developing countries, and from North America and Asia.

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Conflicts of Interest

None declared

Key Points

- This meta-analysis is the first to summarise the disparate findings on prevalence of impaired glucose regulation in Europe.
- A clear understanding of the prevalence of this condition is necessary for planning of health care provision.
- This meta-analysis found that impaired glucose regulation is common in developed Europe with around 1 in 5 people meeting the criteria for IFG, IGT or both.

References

1. Unwin N, Shaw J, Zimmet P, Alberti KGMM. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. Diabetic Med 2002;19 (9):708-723.

2. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and othe categories of glucose intolerance. Diabetes 1979; 28:1039-1057.

3. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183-1197.

4. American Diabetes Association. Diagnosis and Classification for Diabetes Mellitus. Diabetes Care 2010; 33:S62-S69.

5. World Health Organisation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: Report of WHO/IDF consultation. Geneva: World Health Organisation, 2006.

6. Davies MJ, Tringham JR, Troughton J, Khunti KK. Prevention of Type 2 diabetes mellitus. A review of the evidence and its application in a UK setting. Diabetic Med 2004; 21:403-414.

7. The DECODE Study Group. Age- and Sex-Specific Prevalence of Diabetes and Impaired Glucose Regulation in 13 European Cohorts. Diabetes Care 2003; 26:61-69.

8. Stroup D, Berlin J, Morton S, Olkin I, Williams G, Rennie D, et al. Meta-analysis of observational studies in epidemiology. A proposal for reporting. J Am Med Assoc 2000; 283:2008-2012.

9. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-1053.

10. Tabák A, Herder C, Rathmann W, Brunner E, Kivimäk M. Prediabetes: a high risk state for diabetes development. Lancet 2012; 379: 2279-2290.

11. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in healthcare. York: Centre for Reviews and Dissemination, 2009.

12. World Health Organisation. WHO Expert Committee on Diabetes Mellitus Second Report. Technical Report Series 646. Geneva: World Health Organisation, 1980.

13. World Health Organisation. Diabetes Mellitus. Report of a WHO study group. Technical Report Series 727. Geneva: World Health Organisation, 1985.

14. Genuth S, Alberti K, Bennett P, Buse J, Defronzo R, Kahn R, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26:3160-3167.

15. World Health Organisation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Geneva: World Health Organisation, 1999.

16. Joanna Briggs Institute. The Joanna Briggs Institute reviewer's manual. The systematic review of prevalence and incidence data. Adelaide: Joanna Briggs Institute, 2014.

17. Lipsey M, Wilson D. Practical meta-analysis. California: Sage, 2001.

18. Heine RJ, Nijpels G, Mooy JM. New data on the rate of progression of impaired glucose tolerance to NIDDM and predicting factors. Diabet Med 1996; 13:S12-S14.

19. Mooy JM, Grootenhuis PA, De Vries H, Valkenburg HA, Bouter LM, Kostense PJ, et al. Prevalence and determinants of glucose intolerance in a Dutch Caucasian population: the Hoorn Study. Diabetes Care 1995; 18:1270-1273.

20. Borch-Johnsen K, Colagiuri S, Balkau B, Glümer C, Carstensen B, Ramachandran A, et al. Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycaemia. Diabetologia 2004; 47: 1396-1402.

21. Eliasson M, Lindahl B, Lundberg V, Stegmayr B. No increase in the prevalence of known diabetes between 1986 and 1999 in subjects 25-64 years of age in northern Sweden. Diabetic Med 2002; 19:874-880.

22. Tuomilehto J, Korhonen HJ, Kartovaara L, Salomaa V, Stengard JH, Pitkanen M, et al. Prevalence of diabetes mellitus and impaired glucose tolerance in the middle-aged population of three areas in Finland. Int J Epidemiol 1991; 20:1010-1017.

23. Wikström K, Lindström J, Tuomilehto J, Saaristo TE, Korpi-Hyövälti E, Oksa H, et al. Socio-economic differences in dysglycemia and lifestyle-related risk factors in the Finnish middle-aged population. Eur J Public Health 2011; 21:768-774.

24. Forouhi NG, Luan J, Hennings S, Wareham NJ. Incidence of Type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990-2000. Diabet Med 2007; 24:200-207.

25. Andersson S, Ekman I, Friberg F, Daka B, Lindblad U, Larsson CA. The association between self-rated health and impaired glucose tolerance in Swedish adults: a cross-sectional study. Scand J Prim Health Care 2013; 31:111-118.

26. Brohall G, Behre CJ, Hulthe J, Wikstrand J, Fagerberg B. Prevalence of diabetes and impaired glucose tolerance in 64-year-old Swedish women: experiences of using repeated oral glucose tolerance tests. Diabetes Care 2006; 29:363-367.

27. Castell C, Tresserras R, Serra J, Goday A, Lloveras G, Salleras L. Prevalence of diabetes in Catalonia (Spain): an oral glucose tolerance test-based population study. Diabetes Res Clin Pract 1999; 43:33-40.

28. Chaturvedi N, McKeigue PM, Marmot MG. Relationship of glucose intolerance to coronary risk in Afro-Caribbeans compared with Europeans. Diabetologia 1994; 37:765-772.

29. Cruickshank JK, Cooper J, Burnett M, MacDuff J, Drubra U. Ethnic differences in fasting plasma C-peptide and insulin in relation to glucose tolerance and blood pressure. Lancet 1991; 338:842-847.

30. Garancini MP, Calori G, Ruotolo G, Manara E, Izzo A, Ebbli E, et al. Prevalence of NIDDM and impaired glucose tolerance in Italy: an OGTT-based population study. Diabetologia 1995; 38:306-313.

31. Hiltunen L, Luukinen H, Koski K, Kivelä SL. Prevalence of diabetes mellitus in an elderly Finnish population. Diabet Med 1994; 11:241-249.

32. Larsson H, Ahrén B, Lindgärde F, Berglund G. Fasting blood glucose in determining the prevalence of diabetes in a large, homogeneous population of Caucasian middle-aged women. J Intern Med 1995; 237:537-541.

33. Mykkänen L, Laakso M, Uusitupa M, Pyörälä K. Prevalence of diabetes and impaired glucose tolerance in elderly subjects and their association with obesity and family history of diabetes. Diabetes Care 1990; 13:1099-1105.

34. Rajala U, Keinänen-Kiukaanniemi S, Uusimäki A, Reijula K, Kivelä,S.L. Prevalence of diabetes mellitus and impaired glucose tolerance in a middle-aged Finnish population. Scand J Prim Health Care 1995; 13:222-228.

35. Tuomilehto J, Nissinen A, Kivelä,S.L., Pekkanen J, Kaarsalo E, Wolf E, et al. Prevalence of diabetes mellitus in elderly men aged 65 to 84 years in eastern and western Finland. Diabetologia 1986; 29:611-615.

36. Unwin, N, Harland, J, White, M, Bhopal, R, Winocour, P, Stephenson, P, et al. Body mass index, waist circumference, waist-hip ratio, and glucose intolerance in Chinese and Europid adults in Newcastle, UK. J Epidemiol Community Health 1997; 51:160-166.

37. Verrillo A, de Teresa A, La Rocca S, Giarrusso PC. Prevalence of diabetes mellitus and impaired glucose tolerance in a rural area of Italy. Diabetes Res 1985 2:301-306.

38. Almoosawi S, Cole D, Nicholson S, Bayes I, Teucher B, Bates B, et al. Biomarkers of diabetes risk in the National Diet and Nutrition Survey rolling programme (2008-2011). J Epidemiol Community Health 2014; 68:51-56.

39. Baena-Diez JM, Elosua R, Cano JF, Masia R, Sala J, Marrugat J, et al.Waist circumference and impaired fasting glucose screening in a Mediterranean population. Diabetes Res Clin Pract 2009; 86:e12-e14.

40. Bernal-Lopez M, Santamaría-Fernandez S, Lopez-Carmona D, Tinahones FJ, Mancera-Romero J, Peña-Jimenez D, et al. HbA1c in adults without known diabetes from southern Europe. Impact of the new diagnostic criteria in clinical practice. Diabet Med 2011; 28:1319-1322.

Tables

Table 2 Mean prevalence of IGT by several moderator variables

Variable	k	n	Prevalence	95% CI	Q_B (df)	Q_W (df)	I
Age							
18 and over	8	15,048	9.4	7.1-12.4	19.15 (2)*	198.58 (7)*	
30-65	23	45,828	11.8	9.8-14.2		1077.06 (22)*	
66+	4	2,941	25.1	17.8-34.1		72.97 (3)*	
Diagnostic Criteria							
1. 2hPG 7.8-<11.1mmol/l	2	2,951	7.4	5.7-9.6	19.9 (3)*	3.86 (1)*	
2. FPG <8.0mmol/l and 2hPG 8.0-<11.0mmol/l	8	10,047	19.7	13.9-27.2		361.41 (7)*	
3. FPG<7.8mmol/l and 2h 7.8-<11.1mmol/l	19	43,722	10.3	8.6-12.2		704.38 (18)*	
4. FPG <7.0mmol/l and 2hPG 7.8-<11.1mmol/l	2	3,678	13.9	7.6-24.2		49.83 (1)*	
Quality Category							
1 – Higher	13	21,651	12.8	10.3-15.7	0.59 (2)	338.8 (12)*	
2	12	25,686	11.5	9.3-14		370.82 (11)*	
3 – Lower	10	16,480	12.8	8-20		992.21 (9)*	
Country							
Denmark	1	6,784	12	11.2-12.8	43.46 (8)*	0.00 (0)	

Finland	8	12,007	19.9	14.8-26.2	348.05 (7)*
Germany	2	3,006	10.4	3.9-24.7	72.45 (1)*
Italy	3	3,870	6.9	5.4-8.7	7.9 (2)*
Netherlands	1	2,378	10.3	9.1-11.6	0.00 (0)
Portugal	1	5,167	12.6	11.7-13.5	0.00 (0)
Spain	7	11,817	9.5	7.0-12.7	151.38 (6)*
Sweden	5	9,849	14	8.1-23	329.68 (4)*
UK	7	9,659	11.1	8.6-14.3	79.9 (6)*

* $p<0.05$; k: number of studies; n: total sample size; Q_B: between study homogeneity statistic; Q_W: within study homogeneity statistic; I^2 proportion of variability within categories due to heterogeneity rather than sampling error.

Table 3 Weighted multiple regression for IGT prevalence

	β	95% CI	$Q_{(B)}$ (df)
Age			
18 +	-	-	2.25 (2)
30-65	0.25	-0.28- 1.01	
66+	0.72	-0.29- 1.72	
Diagnostic Criteria			
1) 2hPG 7.8-<11.1mmol/l	0.49	-1.05-2.02	10.41 (3)*
2) FPG <8.0mmol/l and 2hPG 8.0-<11.0mmol/l	0.72	-0.29-1.72	
3) FPG<7.8mmol/l and 2hPG 7.8-<11.1mmol/l	0.09	-0.94-1.12	
4) FPG <7.0mmol/l and 2hPG 7.8-<11.1mmol/	-	-	
Country			
Denmark	0.81	-0.42-2.05	7.44 (8)
Finland	0.96^	-0.04-1.96	
Germany	0.65	-0.43-1.74	
Italy	-	-	
Netherlands	0.73	-0.88-2.34	
Portugal	1.12	-0.33-2.57	
Spain	0.53	-0.61-1.68	
Sweden	0.74	-0.25-1.74	

UK	0.38	-0.62-1.38

* $p<0.05$; ^ marginally significant $p=0.0588$; p Q_B: between study homogeneity statistic;

Table 4 Mean prevalence of IFG in men and women by several moderator variables

Variable	k	N	Prevalence	95% CI	Q_B (df)	Q_W (df)	I
			Men				
Age							
18 and over	6	5,548	10	6.6-14.8	0.13 (2)	121.7 (5)*	
30-65	7	8,480	10.6	8.7-12.9		55.67 (6)*	
66+	2	7,385	8.9	2-3.2		298.06 (1)*	
Diagnostic Criteria							
1) FPG 5.6-6.9mmol/l	2	2,298	13	4.8-30.6	0.37(2)	56.13 (1)*	
2) FPG 6.1-6.9mmo/l	8	14,668	10.7	7.7-14.8		306.42 (7)*	
3) FPG 6.1-6.9 and 2hPG <7.8mmo/l	4	3,999	9.7	6.4-14.3		52.87 (3)*	
Quality Category							
1 – Higher	6	6,685	10.6	8.7-12.8	0.09 (2)	30.24 (5)*	
2	5	8,523	10.9	7.5-15.4		129.52 (4)*	
3 – Lower	4	6,205	9.4	3.7-21.8		298.73 (3)*	
Country							
Finland	2	2,320	11.6	8.6-15.3	136.74 (8)*	6.39 (1)*	
France	3	6,177	7.5	3.6-14.9		111.53 (2)*	
Germany	1	896	4.2	3.1-5.7		0.00 (0)	

Greece	1	1,514	20.5	18.5-22.6		0.00 (0)
Italy	1	2,240	12.2	10.9-13.6		0.00 (0)
Netherlands	1	2,378	12	10.8-13.4		0.00 (0)
Spain	2	752	6.1	1.9-18.4		15.4 (1)*
Sweden	1	359	10.6	7.8-14.2		0.00 (0)
UK	3	4,777	14.4	11-18.8		14.64 (2)*
Variable	**k**	**n**	**Prevalence**		**Q_B (df)**	**Q_W (df)**
			Women			
Age						
18 and over	6	6,685	6.5	4.4-9.7	0.96 (2)	91.2 (5)*
30-65	6	6,169	5.2	3.9-6.8		31.32 (5)*
66+	2	9,287	7.3	1.1-35.9		477.71 (1)*
Diagnostic Criteria						
1) FPG 5.6-6.9mmol/l	7	14,610	7.2	3.9-13	1.27 (2)	549.58 (6)*
2) FPG 6.1-6.9mmo/l	2	2,846	6.5	1.8-20.8		62.61 (1)*
3) FPG 6.1-6.9 and 2hPG <7.8mmo/l	4	4,103	4.7	3.0-7.4		30.93 (3)*
Quality Category						

1 – Higher	5	4,977	5.9	3.9-9.1	0.06 (2)	47.09 (4)*
2	5	8,298	6.3	3.0-12.7		287.22 (4)*
3 – Lower	4	8,866	5.5	2.3-12.4		206.1 (3)*
Country						
Finland	2	2,595	5.1	4.3-6	119.82 (7)*	0.12 (1)
France	3	8,647	3.8	2.4-5.9		29.57 (2)*
Germany	1	757	1.9	1.1-3.2		0.00 (0)
Greece	1	1,528	12	10.5-13.7		0.00 (0)
Italy	1	2,497	9.9	8.8-11.1		0.00 (0)
Spain	2	967	4.7	1.9-11.3		9.46 (1)*
Sweden	1	382	6.3	4.3-9.2		0.00 (0)
UK	3	4,771	10.6	5.6-19.2		56.12 (2)*

* $p<0.05$; k: number of studies; n: total sample size; Q_B: between study homogeneity statistic; Q_W: within study homogeneity statistic; I^2 proportion of variability within categories due to heterogeneity rather than sampling error.

Table 5 Mean prevalence of combined IGT and IFG by several moderator variables

Variable	k	n	Prevalence	95% CI	Q_B (df)	Q_W (df)	I
Age							
18 and over	4	9,959	3.5	2.5-4.7		21.53 (3)*	
30-65	6	14,605	1.9	1.5-2.5	7.94 (2)*	24.88 (5)*	
66+	1	499	2.7	1.6-4.6		0.00 (0)	
Quality Category							
1 – Higher	2	6,077	3.2	1.7-6	1.63 (2)	12.5 (1)*	
2	3	5,908	1.8	1-3.4		21.95 (2)*	
3 – Lower	6	13,080	2.6	1.9-3.6		42.26 (5)*	
Country							
Finland	2	3,217	1.9	1.1-3.4	15.12 (5)*	3.56 (1)*	
Germany	1	1,653	1.2	0.8-1.9		0.00 (0)	
Italy	1	919	2.1	1.3-3.3		0.00 (0)	
Portugal	1	5,167	2.4	2-2.9		0.00 (0)	
Spain	4	7,882	3.4	2.5-4.7		19.79 (3)*	
UK	2	6,225	2.4	1.2-4.5		14.2 (1)*	

* $p<0.05$; k: number of studies; n: total sample size; Q_B: between study homogeneity statistic; Q_W: within study homogeneity statistic; I^2 proportion of variability within categories due to heterogeneity rather than sampling error.