Prevention of type 2 diabetes in high risk groups: epidemiology, progression rates and patient views and experiences.

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Abstract

Background: People with gestational diabetes mellitus (GDM) and impaired glucose regulation (IGR) are at increased risk of developing type 2 diabetes but lifestyle change can help to delay or prevent type 2 diabetes in these groups.

Aims: This thesis comprises five publications which inform the development of lifestyle interventions for people with IGR and GDM by describing the epidemiology, progression to type 2 diabetes, and patient views and perceptions associated with these conditions.

Methods: Publications one and two used systematic review and meta-analysis methods to describe the prevalence of IGR and GDM in Europe. A retrospective cohort design utilising routinely collected health care data from one region in Scotland was used in publications three and four to describe the incidence of IGR, and the progression from GDM and IGR to type 2 diabetes. Publication five explored women's perceptions and experiences of GDM using semi-structured interviews informed by behaviour change theory.

Results: Mean prevalence of IGR and GDM in developed Europe was 22.3% and 5.4% respectively. Rates of progression to type 2 diabetes were 9% in a mean time of 34 months for IGR and 25% in a mean time of eight years for GDM. Older people with IGR living in deprived areas and women with GDM who were overweight and with higher fasting plasma glucose levels were at most risk of developing type 2 diabetes. Publication five highlighted how perceptions about the consequences of GDM and timeline and consequences of type 2 diabetes may be linked to the lifestyle change women make after diagnosis of GDM and their lack of success in maintaining these changes postnatally.

Conclusions: This thesis provides a clear understanding of the prevalence of IGR and GDM, rates of progression to type 2 diabetes, and patient views and perceptions on which to base intervention planning and health care delivery.

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Preface

This PhD submission includes five papers published in peer reviewed journals that report on a series of related empirical studies (see Table 1 for references). These studies focus on two groups who are at high risk of developing type 2 diabetes; specifically, people with impaired glucose regulation and women who have had gestational diabetes mellitus. Together the publications inform the development of interventions to prevent type 2 diabetes in these two groups. Publications one to four describe the epidemiology of impaired glucose regulation and the rate of progression from impaired glucose regulation and gestational diabetes mellitus to type 2 diabetes. Publications five explored knowledge and perceptions held by people with gestational diabetes mellitus about their condition.

The studies reported in these publications were conducted over a seven-year period during the period of PhD registration. I was first author on all five publications in this thesis, but each publication had at least two authors in addition to myself as the first author. As the first author on these publications I took the lead in designing the research, day to day running of projects, conducting fieldwork, carrying out analyses and writing publications. However, I was assisted by my co-authors in various aspects of these projects. Appendix 1 outlines author contributions for each publication.

Chapter one sets the context for the thesis by providing an overview of type 2 diabetes, IGR, and GDM, and discusses the evidence for interventions to prevent progression to type 2 diabetes in high risk individuals. The first chapter concludes by outlining the gaps in the literature that will be addressed by the publications in this thesis. Chapter two provides general background to the methods used in this thesis. The publications are included in the thesis in chapters three (publication one), four (publication two), five (publication three), six (publication four) and seven (publication five). These publications are presented verbatim except for changes to abbreviations, table and figure numbering, and referencing format which were made to ensure consistency with the rest of the thesis. Each of these publication chapters is concluded by a critique of the research and methods in the publication and discussion of ethical considerations where relevant. Chapter eight presents a comparison of the publications to other literature, discussion of their contribution to the field, and implications for development of interventions to prevent type 2 diabetes.

Table 1: List of full references for publications

Publication One	**Eades, C.,** France, E. and Evans, J.M.M. (2016) Prevalence of impaired glucose regulation: A meta-analysis. *European Journal of Public Health,* 26 (4), pp. 699-706.
Publication Two	**Eades, C.,** Cameron, D. and Evans, J.M.M. (2016) Prevalence of gestational diabetes in Europe: a meta-analysis. *Diabetes Research and Clinical Practice,* 129, pp. 173-181.
Publication Three	**Eades, C.,** Leese, G.P. and Evans, J.M.M. (2014) Incidence of impaired glucose regulation and progression to type 2 diabetes mellitus in the Tayside region of Scotland. *Diabetes Research and Clinical Practice,* 104 (1), pp. e16-e19.
Publication Four	**Eades, C.,** Styles, M., Leese, G.P., Cheyne, H. and Evans, J.M.M. (2015) Progression from gestational diabetes to type 2 diabetes in one region of Scotland: an observational follow up study. *BMC Pregnancy and Childbirth,* 15, 11. Available: https://doi.org/10.1186/s12884-015-0457-8 [Accessed 1 November 2018].
Publication Five	**Eades, C.,** France, E. and Evans, J.M.M. (2018) Postnatal experiences, knowledge and perceptions of women with gestational diabetes. *Diabetic Medicine,* 35 (4), pp. 519-529.

Chapter one: Background

1.1 Type 2 diabetes

Diabetes mellitus is a group of metabolic disorders characterised by blood glucose levels that are persistently raised above the normal range. There are four types of diabetes, each with different aetiologies: type 1 diabetes, type 2 diabetes, specific types of diabetes due to other causes (e.g. genetic defects) and gestational diabetes mellitus (GDM; WHO 2016). Type 2 diabetes is the most common, accounting for around 88% of diabetes diagnoses in Scotland (Scottish Diabetes Survey Monitoring Group 2017). In type 2 diabetes elevated blood glucose levels occur because of impairment in the cells that produce insulin, a hormone that controls blood glucose levels, and a cellular resistance to the action of insulin (Kahn et al. 2014).

The metabolic changes seen in type 2 diabetes are associated with a number of serious health complications including cardiovascular and cerebrovascular disease, renal failure, neuropathy, peripheral vascular disease and visual problems. As a result, people with type 2 diabetes in England and Wales have a 28.4% additional risk of death and died on average 6 years earlier compared to people without diabetes (Healthcare Quality Improvement Partnership 2017; Emerging Risk Factors Collaboration 2011). Compared to people without diabetes, people with type 2 diabetes are 20 times more likely to be blind, 40 times more likely to have an amputation, twice as likely to suffer a myocardial infarction and twice as likely to have a stroke (Donnelly et al. 2000; Emerging Risk Factors Collaboration 2010). The psychological impact of type 2 diabetes is also considerable; people with diabetes are two to three times more likely to suffer depression, have higher anxiety rates and lower quality of life than people without diabetes (Colagiuri et al. 2006). In addition to reducing the length and quality of life, diabetes places a considerable burden on the National Health Service (NHS) in the UK. Treating diabetes and its complications uses around 10% of the total NHS budget amounting to around £8.8 billion pounds a year (Hex et al. 2012).

Type 2 diabetes is believed to be caused by a complex interaction between genetic and environmental factors and consequently risk factors can be categorised as those that are modifiable, and offer opportunity for preventative intervention, and those that are not modifiable (Nolan et al. 2011). Non-modifiable risk factors for type 2 diabetes include

genetic susceptibility, age, family history and ethnic origin. Although research has identified several genes linked with type 2 diabetes, the potential for genetic risk scores to predict subsequent diabetes is limited (Khan et al. 2014). Furthermore, increasing rates of type 2 diabetes in populations with relatively stable gene pools point to the importance of other factors in the development of type 2 diabetes (Wild et al. 2004). It is suggested that increasing prevalence is driven partly by ageing populations but also by global increases in the rates of overweight and obesity (Wild et al. 2004; Danaei et al. 2011).

Obesity and physical activity are the two main modifiable risk factors for type 2 diabetes. The relationship between obesity and type 2 diabetes is well established in both cross sectional and prospective studies (Wild and Byrne 2006; Prospective Studies Collaboration 2009). In Scotland, around 87% of people with type 2 diabetes have a Body Mass Index (BMI; weight in kilograms divided by the square of height in metres) of over 25 meaning they are classed as overweight or obese (Scottish Diabetes Survey Monitoring Group 2017). Although physical inactivity is associated with obesity, the relationship between physical activity and type 2 diabetes is only partially mediated by obesity (Aune et al. 2015; Smith et al. 2016). Evidence suggests that the increased insulin sensitivity brought about by physical activity may also partly explain the relationship between physical activity and type 2 diabetes (Schulze and Hu 2005).

The association between obesity and type 2 diabetes has meant that the global rise in obesity rates has been mirrored with a similar increase in rates of type 2 diabetes, with the result that type 2 diabetes is now considered a global epidemic (Wild et al. 2004). The International Diabetes Federation (Cho et al. 2018) estimates that there are 451 million adults worldwide with type 2 diabetes compared to an estimate of 171 million in 2000 (Wild et al. 2004). The IDF predicts that this figure will rise to 642 million by 2040 and it is thought that type 2 diabetes will increasingly affect people under the age of 65 (King et al. 1998; Global Burden of Disease Study 2013 Collaborators 2015). This increase among those of working age will further increase the financial burden of type 2 diabetes through the indirect costs to the economy associated with decreased productivity (Breton et al. 2013).

1.2 Prevention of type 2 diabetes

Evidence regarding the increasing rates of type 2 diabetes and the associated personal and financial burden provides a clear rationale for preventative efforts. The NHS in England has recognised this and highlighted diabetes prevention as one of four priority areas (NHS 2014). There are two general strategies for the prevention of ill health that are widely recognised: the high-risk approach, where people at high risk of disease or ill health are identified and targeted, and the whole population approach, in which population-wide changes to risk factors are made (Rose et al. 2008). In a consensus statement on diabetes prevention the IDF suggested that both high risk and whole population approaches should be taken for the prevention of type 2 diabetes (Alberti et al. 2007). Each strategy has its merits and limitations, but to date the majority of research on type 2 diabetes prevention has focused on prevention in high risk groups (Alberti et al. 2007). Furthermore, clinical guidance published by The National Institute for Health and Care Excellence (NICE) in the UK clearly states that people at high risk of type 2 diabetes should be offered lifestyle interventions (NICE 2012).

Several well-designed randomised controlled trials (RCTs) have investigated the effectiveness of lifestyle and pharmacological interventions in high risk groups and have shown that the onset of type 2 diabetes can be prevented or at least delayed (Albright and Gregg 2013). A systematic review and meta-analysis of RCTs reported that lifestyle interventions reduced incidence of type 2 diabetes by around half and were as effective as pharmacological interventions (Gillies et al. 2007).

One of the largest RCTs of diabetes prevention to date is the Diabetes Prevention Program (DPP). This was a multicentre trial conducted in 3,234 adults with blood glucose levels that were elevated, but not diagnostic of type 2 diabetes, in the United States (DPP research group 2002). The DPP randomly assigned participants to receive an intensive lifestyle intervention or pharmacological intervention and compared these to a group receiving a placebo. The aim of the lifestyle intervention was to reduce body weight by at least 7% and for participants to engage in moderate intensity physical activity for at least 150 minutes a week. Delivery of the lifestyle intervention was flexible but involved 16 face to face lessons over a 24-week period covering diet, exercise and behaviour modification followed by monthly individual and group sessions. The lifestyle intervention was found to reduce incidence of type 2 diabetes by 58% over an average

follow up period of 2.8 years and by 34% over a 10 year follow period. In comparison, pharmacological intervention reduced incidence by 31% over 2.8 years and 18% over 10 years (DPP research group 2009). Analysis of a subset of 350 women with a self-reported history of GDM showed that lifestyle intervention reduced incidence of type 2 diabetes by 35% and pharmacological intervention by 40% over 10 years (DPP research group 2015).

Although the efficacy of lifestyle interventions for preventing type 2 diabetes is well established, the lifestyle interventions included in the review by Gillies et al. (2007) were very resource intensive leading to questions about the feasibility of translating these findings to settings like primary care. Translational research attempts to answer these types of questions through assessment of smaller scale research in real world settings where resources are limited (Garfield et al. 2003). A synthesis of translational research on lifestyle interventions for the prevention of type 2 diabetes conducted by Johnson et al. (2013) included 17 studies which were conducted in a range of settings and based on either the DPP or Finnish Diabetes Prevention Study protocols with modifications to increase feasibility and access for the specific setting under study. For example, the most common modification was to deliver the intervention over fewer sessions. All but one of these studies reported weight loss than was greater in the intervention group compared to the control group. The authors conclude that there is potential for less intensive interventions to have an impact on future progression to diabetes in high risk individuals.

1.3 Impaired glucose regulation

The group of people most commonly targeted by prevention programs such as the DPP are those with impaired glucose regulation (IGR). People with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), known collectively as IGR, have blood glucose levels that are higher than normal but do not meet the diagnostic criteria for type 2 diabetes mellitus. Empirical estimates of prevalence of IGR vary widely but is generally accepted that around 15% of adults in developed countries have some type of IGR (WHO 2006). People with IGR are at an increased risk of developing type 2 diabetes and at increased risk of all cause and cardiovascular mortality (Unwin et al. 2002; Evans et al. 2015). Around 5 to 10% of people with IGR will develop type 2 diabetes annually but it is thought that in the longer term the majority will go on to develop type 2 diabetes (Tabak et al. 2012). As an intermediate stage between normal glucose tolerance and type 2

diabetes, it is not surprising that the same risk factors are associated with IGR as with type 2 diabetes (Nathan et al. 2007).

IGT was first formally recognised in published diagnostic guidance for diabetes in 1979 while IFG was not recognised until 1997 with the precise glucose levels used to diagnose IFG and IGT depending upon the specific guidance used (National Diabetes Data Group [NDDG] 1979; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). In the most current guidance from the American Diabetes Association (ADA 2010) and the WHO (2006), 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).

1.4 Gestational diabetes mellitus

Women who have had gestational diabetes mellitus (GDM) are another group that have been the target of type 2 diabetes prevention interventions. GDM is defined as glucose intolerance that is first diagnosed in pregnancy and which increases the risk of complications for both mother and child during pregnancy (Buckley et al. 2012). Although normal glucose regulation usually returns shortly after delivery, the consequences of GDM extend far beyond pregnancy with affected women having a seven-fold increased risk of type 2 diabetes compared to women who have not had GDM. Rates of type 2 diabetes after a diagnosis of GDM vary depending on the population and length of follow up but have been reported to be as high as 70% (Ferrara 2007; Kim et al. 2002). Women are thought to be at the greatest risk of developing type 2 diabetes in the first five years following a pregnancy with GDM, with incidence plateauing at around 10 years (Kim et al. 2002).

It is estimated that GDM affects around 7% of all pregnancies worldwide although prevalence is difficult to estimate because of a lack of accepted diagnostic criteria (ADA 2003). There are several diagnostic criteria in use internationally which outline different recommendations on the screening of women for testing, how testing should be conducted, and the precise blood glucose levels that should be considered as a diagnostic

of GDM (Buckley et al. 2012). A further complication in assessing GDM prevalence comes from women with undiagnosed pre-gestational diabetes. Data from the National Health and Nutrition Examination Survey conducted between 1999 and 2002 in the US shows that around 1% (95% Confidence Interval 0.1-3.1%) of women aged 20 to 39 have undiagnosed diabetes (Cowie et al. 2006). Although the definition of GDM as glucose intolerance first diagnosed in pregnancy means that some women with undiagnosed pre-gestational diabetes will be incorrectly diagnosed with GDM, this research suggests that the number of women in this category would be small.

In Scotland, the Scottish Intercollegiate Guidelines Network (SIGN 2014) guidance forms the basis of clinical diagnoses of GDM and is aligned with the International Association of Diabetes and Pregnancy Study Group recommendations (IADPSG 2010). The most recent SIGN guideline recommends that women be assessed for the presence of risk factors at their first antenatal visit and all women with risk factors have Haemoglobin A1c (HbA1c) or FPG measured at this time, followed by a 75g OGTT at 24 weeks. Established risk factors for GDM include increased maternal age, obesity, ethnic origin and family history of diabetes (Bellamy et al. 2009). Women assessed as low risk are recommended to have an FPG at 24-28 weeks. GDM is diagnosed according to the following thresholds: an FPG of 5.1 and over, or plasma glucose of 10mmol/l and higher 1 hour after a 75g OGTT, or 8.5mmol/l and above 2 hours after OGTT.

1.5 Gaps in the literature

The evidence discussed up to this point shows that type 2 diabetes is a growing public health concern and that there is a need for preventative interventions to reduce the personal and financial burden of this condition. A diagnosis of IGR and GDM offer an ideal opportunity for the prevention of type 2 diabetes. However, there are a number of gaps in the literature that need to be addressed in order for this opportunity to be successfully realised. The publications included in this thesis aim to address these gaps to inform the development of interventions to prevent type 2 diabetes.

Epidemiology of impaired glucose regulation and gestational diabetes mellitus

In order to plan interventions and health care provision it is important to have a clear understanding of the epidemiology of IGR and GDM. Estimates of both IGR and GDM

vary widely from study to study. For example, a study assessing IGR prevalence in 13 population groups in nine European countries reported estimates of IGR that ranged from 3.2% to 64.2% (DECODE Study Group 2003). This variation is likely to be due to several factors such as the distribution of age and sex in the sample, differences in the data collection methodology, and differences 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, the first publication in this thesis reports a meta-analysis of observational studies assessing the prevalence or incidence of IGR in the general population of adults in developed countries in Europe. This is the first meta-analysis to bring together all the evidence relating to IGR prevalence in Europe and offers a valuable contribution to the literature by making sense of disparate findings.

In a review of studies assessing prevalence of GDM in Europe the majority of studies reported prevalence estimates of GDM in pregnant women of between 2 and 6% (Buckley et al. 2012). Assessment of GDM prevalence is made difficult by a lack of universally accepted diagnostic criteria (Buckley et al., 2012). While the review by Buckley et al. (2012) provides a useful starting point for understanding GDM prevalence, it did not employ systematic review methods or conduct a meta-analysis. The second publication in this thesis reports a systematic review and meta-analysis of GDM prevalence in developed countries in Europe. This is the first systematic review and meta-analysis to bring together evidence on GDM prevalence in Europe.

Progression to type 2 diabetes

In planning interventions and health care provision it is also important to understand the number of high-risk individuals that are currently in contact with health services, and the rate and time scale of progression to type 2 diabetes in these individuals. If the lifestyle interventions for prevention of type 2 diabetes are to be translated into settings such as primary care, it is important to understand the size of the potential population that could be targeted by such an intervention without conducting additional screening. In addition, assessing the rate and timescale of progression to type 2 diabetes would help in the planning of these interventions. The third publication in this thesis reports on incidence of IGR and progression to type 2 diabetes in the Tayside region of Scotland; this publication is the first to investigate incidence of IGR and progression to type 2 diabetes in the UK. The fourth publication included in this thesis outlines progression from GDM

to type 2 diabetes in the Tayside region of Scotland and is the first published study to investigate this in Scotland.

Patient beliefs and perceptions

While these studies provide a useful starting point for understanding the perceptions people with IGR, there is a clear need for further research in the UK. Having a clear understanding of patient beliefs and perceptions about IGR can help to ensure that interventions are appropriately tailored and target those beliefs that may be a barrier (or facilitator) to behaviour change.

Lifestyle interventions have typically included women with GDM alongside other high-risk groups, rather than specifically targeting them. The DPP included over 2000 women with GDM but found that women with a history of GDM showed poorer engagement in lifestyle change compared to women without a history of GDM (Ratner et al. 2008). In recent years there have been several studies examining lifestyle interventions specifically for women with prior GDM but many of these have experienced challenges with recruitment (Gilinsky et al. 2015). The challenges facing women with GDM in making lifestyle changes are potentially quite different to those facing other high-risk groups, such as people with IGR. It is therefore important that the beliefs of women about GDM and about making lifestyle changes are assessed to ensure that interventions are appropriately tailored to women with GDM and well received by them.

A review of research assessing perceptions among women with GDM identified no research conducted in the UK (Parsons et al. 2014). Since this review was carried out there have been two studies conducted in in the UK and one in Ireland (Lie et al. 2013; McMillan et al. 2018; Tierney et al. 2015). Participants in these studies reported that they were aware of their future risk of type 2 diabetes but did not always act on this. Changes made during pregnancy were motivated by the benefits they would give to their unborn child, but these changes were often not maintained after pregnancy due to several barriers including tiredness and the demands of looking after a young baby.

The Medical Research Council (MRC) guidance on developing complex interventions suggests that an appropriate theoretical basis should be identified at the earliest stages of intervention development (MRC, 2006). It is argued that the use of theory in intervention design increases the likelihood that an intervention will be effective by ensuring that the

causal determinants of behaviour are understood and addressed (Michie et al. 2008). Of the studies included in the review by Parsons et al. (2014), only two were informed by behaviour change theory. These two studies were informed by the health belief model and compared beliefs about GDM in people born in Sweden with people living in Sweden who were born in the Middle East (Hjelm et al. 2005) and Africa (Hjelm et al. 2012). As discussed above, theory is important for understanding the causal determinants of behaviour and aids the development of effective interventions (Michie et al. 2008). There is therefore a need for further research exploring beliefs and perceptions about GDM in the UK context that is underpinned by behaviour change theory. The fifth publication included in this thesis aims to assess perceptions among women with previous GDM in the Scottish context using semi-structured interviews. The fifth publication will build upon the previous research by using behaviour change theory to inform the interviews and analysis.

Chapter two: Methods

The publications included in this thesis used a combination of quantitative and qualitative methods. These two approaches make different fundamental assumptions about the nature of knowledge and involve different research methods. Quantitative research is systematic and concerned with classification of size and number (Pope and Mays 2008). The assumptions about knowledge that quantitative research is based upon originated from a branch of philosophy called Positivism. Positivism values objectivity and argues that only things that are measurable actually exist. It holds the belief that there is an objective truth that exists and that this truth can be discovered and measured. Quantitative studies usually have a research question that needs to be answered or a hypothesis that is accepted or rejected. Attempts are made in quantitative research to reduce bias and subjectivity in order to allow the findings of the research to be generalised (Ross 2012). Quantitative research typically uses probability sampling where a random sample of all potential participants is taken. In probability sampling each person in the population under study has an equal chance of being selected (Ross 2012). The aim of probability sampling is to gather a sample that is representative of the population under study allowing generalisations to be made about the findings beyond the sample (Tillé and Wilhelm 2016).

In contrast, qualitative research attempts to understand people's subjective experiences of the world and how they make sense of these experiences. It asks questions such as what, how and why in order to gain an in depth understanding of human behaviour (Malterud 2001). There are a range of approaches in qualitative research and these are often underpinned by diverse theoretical perspectives. The role of theory in qualitative research has been contentious, with some researchers arguing that qualitative research should be underpinned by a theoretical perspective and others suggesting that the choice of method is as much driven by pragmatic or technical considerations as by a theoretical stance (Brannen 2005; Malterud 2001). Methods used to collect data in qualitative research include observation, interviews, analysis of documents, and analysis of speech or behaviour from recorded sources. These methods typically produce large amounts of data and involve smaller samples than quantitative research (Moser and Korstjens 2018). Qualitative research typically uses non-probability sampling where samples are gathered in way that does not give everyone in the population an equal chance of being selected.

These samples may be selected because they are convenient, readily available or fit the purpose of the study rather than because they are representative of the population under study (Malterud 2001). These samples are not selected with the intention that findings will be generalisable to the wider population but to gain a deeper understanding of the topic under investigation (Pope and Mays 2008).

Although qualitative and quantitative research, and their theoretical underpinnings, have traditionally been posed as opposites with researchers identifying with one or the other, there has been a shift towards researchers using approaches that are driven by the nature of the question being asked. The research conducted in this thesis is based upon a pragmatic approach. Pragmatism originated in the late 1800s in the work of American philosophers Charles Sanders Pierce, William James, John Dewey and George Herbert Mead, and rejects attempts to understand the nature of knowledge and its relationship to reality (Biesta 2010). In a pragmatic approach the value of knowledge is judged by the consequences of this knowledge in action. Rather than ask if knowledge reflects reality, pragmatism asks if the knowledge serves our interests (Cornish and Gillespie 2008). As such, the methods chosen in this thesis were selected for their appropriateness for answering the research questions posed by each publication.

Publications one and two used systematic review and meta-analysis methods. In publications three and four, data linkage and analysis of routinely collected health care data were carried out. Publication five used semi-structured interviews. In terms of the number of people investigated and the level of personal contact with these people, the methods used in publications one to four are at one extreme of the spectrum upon which quantitative and qualitative methods sit, and the methods used in publication five are at the other. However, all these methods are valid and can complement each other if applied to appropriate research questions.

2.1 Systematic review and meta-analysis

Systematic review is a method that aims to identify and synthesise all the existing research on a specific topic by conducting a comprehensive search according to a predetermined method. All existing research that is relevant to the topic or question is included regardless of the direction or magnitude of the results (Klassen et al. 1998). A rigorously conducted systematic review offers an exhaustive summary of existing

evidence, can identify areas where evidence is lacking, and can help to resolve inconsistencies or controversies in the literature. Systematic reviews of observational studies can also help to identify factors that are associated with the outcome of interest (Denison et al. 2013). Limitations of the systematic review method include the difficulty in identifying all potentially relevant publications and variability in the quality of included studies which can limit the utility of the review (Klassen et al. 1998).

The data collected in a systematic review can be observational or experimental and can be synthesised either by narrative synthesis or meta-analysis. Meta-analysis is a statistical technique for combining data from a minimum of two independent studies to provide a single estimate of the outcome of interest (Denison et al. 2013). Where results are in a numerical form it is generally recommended to try to combine them using a meta-analysis although there are situations where a meta-analysis is not possible or recommended. For example, combining studies with different research designs or studies of poor methodological quality is not recommended (Lipsey and Wilson 2000). In these situations, a narrative synthesis is recommended where results are descriptively summarised and relationships within and between studies are analysed (Centre for Reviews and Dissemination [CRD] 2009).

Given the large number of studies available that assess prevalence of IGR and GDM, and the inconsistencies in the findings of these studies, a systematic review was conducted as it offers a way of summarising and making sense of these disparate findings. Meta-analysis allows a single estimate of IGR and GDM prevalence to be produced and for factors that influence this estimate to be explored.

2.2 Linkage of routine data

A broad range of data is routinely collected in health care settings. Examples of data collected by the NHS include hospital bed occupancy, cervical screening rates, provision of contraceptive services, prescription dispensing, laboratory and diagnosis data (Kane et al. 2000). There are a number of arguments for utilising routinely collected data in research. One of the key benefits of routine data is that it is often readily available at a relatively low cost meaning that researchers can avoid the time intensive and costly process of primary data collection (Powell et al. 2003). Routine data can also be more comprehensive than sampled data and includes information on large numbers of patients.

The fact that routine data can be used retrospectively means that data for longer time periods can be gathered more quickly than in primary data collection (Kane et al. 2000). Potential limitations of routine data include that it may not be up to date and may not be complete. Because routine data are collected with a different purpose from that of the research being carried out, there may be key variables of interest missing (Kane et al. 2000).

The limited range of variables sometimes available in routinely-collected data can be addressed through linkage of data. Linkage of routine data refers to the process of linking records from two sources in order to identify pairs of records that belong to the same individual (Bohensky et al. 2010). Linking data allows a range of variables from different databases to be accessed offering a more comprehensive data-set. Linkage can be carried out between two separate data sources or within one source of data to track multiple entries for one individual (Bohensky et al. 2010). There are two commonly used methods of data linkage: deterministic and probabilistic. Deterministic linkage is used where there are unique identifiers such as an NHS number that can be used to match completely with other datasets. Probabilistic linkage is used where a unique identifier is not available and involves matching of other variables that partially identify the individual such as age or sex (Bohensky et al. 2010).

2.3 Semi-structured interviews

The last two decades have witnessed a huge increase in the use of qualitative methods in health research. As discussed at the start of this chapter, qualitative research aims to answer questions such as what, how and why, whereas quantitative research is concerned with classification of size and number (Pope and Mays 2008). The ability of qualitative research to answer these types of questions is one of the key reasons for the decision to use this method in the context of the questions posed by publication five in this thesis. Semi-structured interviews are conducted using an interview guide that contains a set of open-ended questions from which the interviewer or interviewee may diverge in order to pursue something not covered in the guide in more detail (Arthur et al. 2014). The semi-structured format was appropriate for publication five as it is structured enough to ensure that topics of interest are covered, such as theoretical concepts posed by behaviour change theories, while allowing interviewees the freedom to discuss any issues not covered by the interview guide and the theoretical frameworks (Moser and Korstjens 2018).

Once qualitative data have been collected there are several different ways in which they can be analysed. A framework approach was taken/planned for the organisation and analysis of the data collected for publication five (Spencer and Ritchie 2002). This approach was developed by the National Centre for Social Research in the UK and is increasingly being used in health care research (Ritchie et al 2014). Examples of applications of the framework approach in health settings include exploring experiences of Chronic Obstructive Pulmonary Disease, barriers to weight loss in children and factors influencing the use of information technology in the emergency department (Elkington et al. 2004; Murtagh et al 2006; Ayatollahi et al. 2010). The framework approach is relatively structured and allows pre-set objectives and reasoning to inform data collection while still allowing original contributions from participants (Gale et al. 2013). A framework approach is therefore appropriate for publication five given that it is informed by theory and previous research (Pope et al. 2000).

Spencer and Ritchie (2002) describe five key stages in undertaking a framework approach to analysing qualitative data: familiarisation, identifying a thematic framework, indexing, charting, mapping and interpretation. The first stage involves the researcher familiarising themselves with the interview transcripts. Through careful listening to recordings, reading of interview transcripts, and study of field notes the researcher should gain an overview of the range and diversity of the data. During this stage of the analysis, the researcher lists key ideas and themes that arise from the data and records the range of responses and summarise what participants are describing (Spencer and Ritchie 2002; Smith and Firth 2001).

The second stage of the framework approach involves developing an analytical framework. The researcher does this by returning to the notes made during familiarisation and attempts to identify key concepts that can be used to sort the data. The framework draws upon both *a priori* issues, those brought up in interviews via the topic guide, and those that emerge from the participants themselves. Development of the framework requires the researcher to make judgements about meaning, relevance and significance of issues and is an iterative process with refinements being made to the framework as it is applied to data (Spencer and Ritchie 2002).

After development of the framework the next stage of this approach is indexing, where the framework is applied to each transcript in turn. Data are read and annotated using

numerical codes that link back to the framework. As in stage two, indexing requires the researcher to make judgements about the data regarding meaning, relevance and significance. The fourth stage of the framework approach is to called charting and involves removing data from the transcripts and summarising it in a matrix according to the theme that it refers to. The matrix headings and subheadings may come from the framework, research questions or from practical considerations about how best to present the data. Charting involves abstraction and synthesis rather than copying sections of the data verbatim (Spencer and Ritchie 2002).

When all the data have been charted, the final stage of the framework approach is mapping and interpretation of the data set as a whole. During this stage, the researcher reviews and maps the range of things people are saying about a theme in order to propose key underpinning themes or concepts. Finally, the researcher looks for any linkage and patterns between these themes and tries to search for key factors or processes that can account or explain these patterns (Spencer and Ritchie 2002; Gale et al. 2013).

Research using a framework approach can sit anywhere on the inductive-deductive continuum depending on the research question and aims of the study (Gale et al. 2013). Purely inductive approaches to research attempt to generate new knowledge and theories whereas deductive approaches test out existing theories and reasoning (Ross 2012). The approach taken in publication five was a combination of inductive and deductive approaches and was driven by the aims of the research. One of the aims of the semi-structured interviews was to inform the development of lifestyle interventions to prevent type 2 diabetes. As discussed in chapter one, it has been argued intervention design should be informed by theory to ensure that the causal determinants of behaviour are understood and addressed (Michie et al. 2008). As there is extensive research to support various psychological theories of behaviour change for predicting and changing behaviour (Armitage and Conner 2001; Hagger and Orbell, 2003; Hagger et al. 2017), it was decided that the interviews would be informed by these pre-existing theories rather than develop new theory using an inductive approach such as Grounded Theory (Charmaz 2006). However, psychological theories of behaviour change have been criticised for failing to consider several important influences on behaviour such as emotional responses (Sniehotta et al. 2014). Considering these criticisms, it was decided that a combined inductive and deductive approach would be taken when labelling data

during the familiarisation stage of analysis to ensure that important issues arising from the data, as well as from theory, were identified.

Two psychological models were selected to inform the analysis in publication five: the Theory of Planned Behaviour (TPB; Ajzen 1991) and the Self Regulation Model of Illness Behaviour (SRM; Leventhal et al. 1992). The SRM and TPB offer different approaches to understanding behaviour change for prevention of type 2 diabetes with the SRM focusing on patients' beliefs about their health condition (i.e. IGR or GDM and type 2 diabetes) whereas the TPB is concerned with beliefs about the lifestyle behaviours.

The TPB states that voluntary behaviours are largely predicted by our intentions regarding the behaviour. Intentions in turn are determined by our attitude towards the behaviour (our judgement of whether the behaviour is a good thing to do), subjective norms (our judgement of what important others think of the behaviour), and perceived behavioural control (PBC; our expectation of how successful we will be in carrying out the behaviour; Ajzen, 1991).

The SRM proposes that people interpret information about a potential illness to create a 'lay' view or representation of the illness. The coping responses employed by an individual, for example, adhering to treatment regimens and attending appointments, are said to be related to the illness representations they hold and to their appraisal of how successful they perceive the chosen coping responses to be. Illness representations are proposed to be formed around six different themes: identity (label or diagnosis of illness), cause (factors believed to have caused the illness), timeline (expected duration of illness), consequences (expected effects of illness on physical, social and psychological well-being), control/cure (extent to which illness can be controlled/cured) and illness coherence (how well the person understands their illness; Leventhal et al. 1992).

There is no evidence to suggest which model was most appropriate in the context of the questions posed by publication five (Armitage and Conner 2001; Hagger et al. 2017). Both models have been successfully used to understand a wide range of health behaviours and health conditions (Armitage and Conner 2001; Hagger and Orbell, 2003; Hagger et al. 2017). For example, the TPB has been used to inform qualitative research exploring physical activity in parents of young children, walking as treatment for intermittent claudication and non-attendance at diabetes appointments (Hamilton and White 2010;

Galea Holmes et al. 2017; Lawson et al. 2005). Examples of applications of the SRM in qualitative research include to explore women's experiences of myocardial infarction, multimorbidity in long term conditions and help seeking for depression (White et al. 2007; Bower et al. 2012; Rani Elwy et al. 2011). There has also been considerable research assessing interventions that address the beliefs and perceptions outlined by both the TPB and SRM (Hardeman et al. 2010; McSharry et al. 2011; French et al. 2006). As one of the aims of publication five was to inform the development of an intervention, the research supporting the role of these models in intervention development is valuable to publication five.

The SRM has been widely used in understanding self-management of diabetes (Harvey and Lawson 2009). Although the self-management behaviours needed for the control of GDM and diabetes are largely similar, the timeline of GDM is much shorter than diabetes with blood glucose levels returning to normal in most women with GDM postnatally. Since most women with GDM are not considered to have an illness in the postnatal period it may not be appropriate to only use a model of illness, such as the SRM, and as such the TPB was selected to provide a theoretical approach that was not limited to understanding responses to illness. Therefore, both the TPB and SRM were used to inform semi-structured interviews in this thesis with the aim that the SRM would provide an insight into patient's perceptions about IGR, GDM and type 2 diabetes, and that the TPB would provide an understanding of behaviour change in women with GDM .

Chapter three: Prevalence of impaired glucose regulation in Europe (publication one)

Eades, C.E., France, E.F. and Evans, J.M.M. (2016) Prevalence of impaired glucose regulation: A meta-analysis. *European Journal of Public Health*, 26 (4), pp. 699-706.

This paper was published in European Journal of Public Health, a peer reviewed journal with an impact factor of 2.43, and has been cited four times. The journal publishes multidisciplinary research on international public health issues with a focus on the European Region and is ranked 28th out of 157 journals in the Public, Environmental & Occupational Health category of the social science citation index.

The content of the above publication is presented in this chapter followed by a section providing critical reflection on the methods of this paper. A PDF of the published manuscript can be found in appendix 3.

A verbatim copy of publication one starts below.

3.1 Abstract

Background: Impaired glucose regulation (IGR) represents an opportunity to prevent type 2 diabetes. 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 IGR 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 IGR was 22.3%. Mean prevalence of impaired glucose tolerance (IGT) 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 IGT but only diagnostic criteria remained significant in multivariate analysis. Mean prevalence of impaired fasting glucose (IFG) 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 IFG prevalence was country.

Conclusions: This meta-analysis shows a moderate prevalence of IGR in developed Europe with over one in five people meeting the criteria for either IGT, IFG, or both.

3.2 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. These two states, known collectively as impaired glucose regulation (IGR), confer an increased risk of developing type 2 diabetes (Unwin et al. 2002). IGT was first formally recognised in published diagnostic guidance for diabetes in 1979 (NDDG, 1979) while IFG was not recognised until 1997 (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997) with the precise glucose levels used to diagnose IFG and IGT depending upon the specific guidance used. In the most current guidance from the American Diabetes Association (ADA 2010) and the world health organisation (WHO 2006), 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 an 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 diabetes, research has shown that by making lifestyle changes they can prevent or delay progression to type 2 diabetes (Unwin et al. 2002). With prevalence of type 2 diabetes increasing rapidly, a diagnosis of IGR represents an opportunity for intervention to reduce the burden of type 2 diabetes (Davies et al. 2004). 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% (DECODE Study Group 2003). 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.

3.3 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 (Stroup et al. 2000). 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 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 (CEE and JMME or EFF) against the following inclusion criteria:

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).

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.

Study design: observational study, published in English.

All papers were screened by CEE; JMME and EFF 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 diabetes and impaired glucose regulation between developed and developing countries (Wild et al. 2004; Tabak et al. 2012). 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 diabetes, 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 (CEE) using a standardised data extraction form based on the example provided by the centre for reviews and dissemination (CRD 2009). 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. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997); 2) FPG <8.0mmol/l and 2hPG 8.0-<11.0mmol/l (e.g. WHO 1980); 3) FPG<7.8mmol/l and 2h 7.8-<11.1mmol/l (WHO 1985) 4) FPG <7.0mmol/l and 2hPG 7.8-<11.1mmol/l (e.g. WHO 2006). 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. Genuth et al. 2003); 2) FPG 6.1-6.9mmo/l (e.g. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997); 3) FPG 6.1-6.9 and 2hPG <7.8mmol/l (WHO 1999).

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 (2014) 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 (CEE) 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 (Lipsey and Wilson 2000). 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 (Lipsey and Wilson 2000). 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 (DECODE study group 2003).

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.

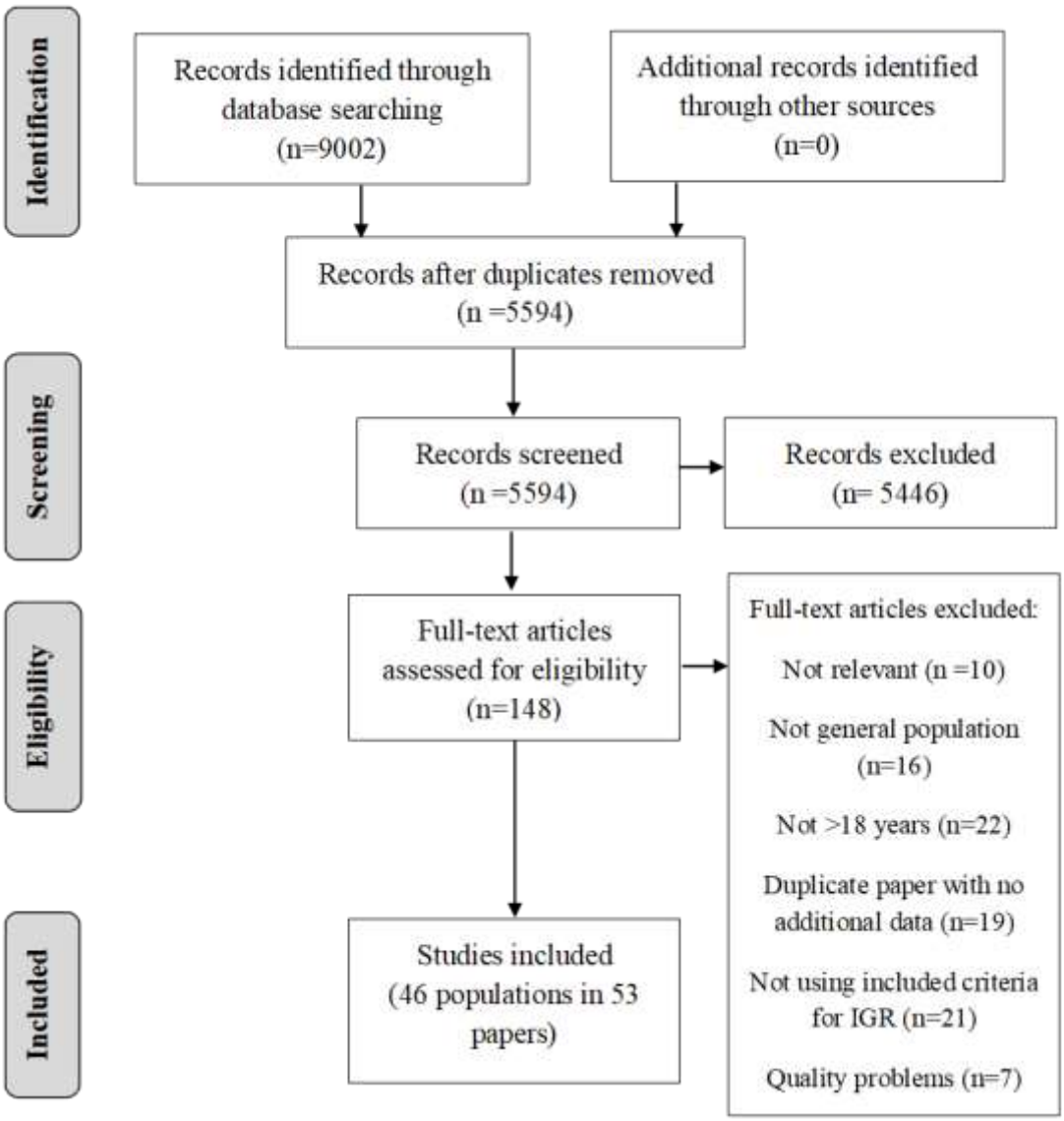
3.4 Results

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: Heine et al. 1996; Mooy et al. 1995; Borch-Johnsen et al. 2004; Eliasson et al. 2002; Tuomilehto et al. 1991; Wikström et al. 2011; Forouhi et al. 2007). These 46 studies included a total of 77,379 participants. The characteristics of the studies included in the review are presented in Table 2 (Appendix 2). Of the 46 studies included, 13 assessed prevalence of IGT (Andersson et al. 2013; Brohall et al. 2006; Castell et al. 1999; Chatuverdi et al. 1994; Cruickshank et al. 1991; Garancini et al. 1995; Hiltunen et al. 1994; Larsson et al. 1995; Mykkänen et al. 1990; Rajala et al. 1995; Tuomilehto et al. 1986; Unwin et al. 1997; Verrillo eta al. 1985), 11 assessed the prevalence of IFG (Almoosawi et al. 2014; Baena-Diez et al. 2009; Bernal-Lopez et al. 2011; Bonaldi et al. 2011; Bourdel-Marchasson et al. 2007; Gasull et al. 2012; Gourdy et al. 2001; Mentoni et al. 2009; Panagiotakos et al. 2007; Thomas et al. 2005; Valverde et al. 2006) and 22 reported the prevalence of both

IFG and IGT (Bennet et al. 2011; Bonora et al. 2004; Boronat et al. 2004; Cederberg et al. 2010; de Pablos-Velasco et al. 2001; de Vegt et al. 1998; Gardete-Correia et al. 2010; Glümer et al. 2003; Harris et al. 2000; Lilja et al. 2013; López et al. 2012; Meisinger et al. 2010; Qiao et al. 2003; Rathmann et al. 2003; Saaristo et al. 2008; Soriguer et al. 2008; Soriguer et al. 2012; Valdés et al. 2007; Webb et al. 2011; Wild et al. 2005; Williams et al. 1995; Ylihärsilä et al. 2005).

Figure 1: Flow diagram showing study selection



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 2 (See appendix 2). Six studies were identified that had two major weaknesses (Baule 2003; Tuescher et al. 2001; Drivsholm et al. 2001; Tamayo-Marco et al. 1997; Croxson and Burden 1998; Aujla et al. 2010): 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 (Papazoglou et al. 1995). 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 (Hiltunen et al.1994; Tuomilehto et al. 1986; Unwin et al. 1997) and one for IFG (Bonora et al. 2004). 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 (Hiltunen et al. 1994; Unwin et al. 1997; Bonora et al. 2004) and one with a sample aged 55 (Tuomilehto et al. 1986).

Mean prevalence of impaired glucose tolerance

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 impaired glucose tolerance

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 3 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).

Table 3: Mean prevalence of IGT by several moderator variables

Variable	K	N	Prevalence	95% CI	Q_B (df)	Q_W (df)	I^2 (%)
Age							
18 and over	8	15,048	9.4	7.1-12.4	19.15 (2)*	198.58 (7)*	96.5
30-65	23	45,828	11.8	9.8-14.2		1077.06 (22)*	98
66+	4	2,941	25.1	17.8-34.1		72.97 (3)*	95.9
Diagnostic Criteria							
1. 2hPG 7.8-<11.1mmol/l	2	2,951	7.4	5.7-9.6	19.9 (3)*	3.86 (1)*	74.1
2. FPG <8.0mmol/l and 2hPG 8.0-<11.0mmol/l	8	10,047	19.7	13.9-27.2		361.41 (7)*	98.1
3. FPG<7.8mmol/l and 2h 7.8-<11.1mmol/l	19	43,722	10.3	8.6-12.2		704.38 (18)*	97.4
4. FPG <7.0mmol/l and 2hPG 7.8-<11.1mmol/l	2	3,678	13.9	7.6-24.2		49.83 (1)*	98
Quality Category							
1 – Higher	13	21,651	12.8	10.3-15.7	0.59 (2)	338.8 (12)*	96.5
2	12	25,686	11.5	9.3-14		370.82 (11)*	97
3 – Lower	10	16,480	12.8	8-20		992.21 (9)*	99.1
Country							
Denmark	1	6,784	12	11.2-12.8	43.46 (8)*	0.00 (0)	0.0
Finland	8	12,007	19.9	14.8-26.2		348.05 (7)*	98
Germany	2	3,006	10.4	3.9-24.7		72.45 (1)*	98.6
Italy	3	3,870	6.9	5.4-8.7		7.9 (2)*	74.7
Netherlands	1	2,378	10.3	9.1-11.6		0.00 (0)	0.0
Portugal	1	5,167	12.6	11.7-13.5		0.00 (0)	0.0
Spain	7	11,817	9.5	7.0-12.7		151.38 (6)*	96
Sweden	5	9,849	14	8.1-23		329.68 (4)*	98.8
UK	7	9,659	11.1	8.6-14.3		79.9 (6)*	92.5

* $p<0.05$; 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.

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 4 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.

Table 4: 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;

Mean prevalence of impaired fasting glucose

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 impaired fasting glucose

As significant differences in IFG prevalence existed between men and women, analyses were conducted and presented separately by gender. Table 5 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.

Table 5: 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^2 (%)
			Men				
Age							
18 and over	6	5,548	10	6.6-14.8	0.13 (2)	121.7 (5)*	95.9
30-65	7	8,480	10.6	8.7-12.9		55.67 (6)*	89.2
66+	2	7,385	8.9	2-3.2		298.06 (1)*	99.7
Diagnostic Criteria							
1) FPG 5.6-6.9mmol/l	2	2,298	13	4.8-30.6	0.37(2)	56.13 (1)*	98.2
2) FPG 6.1-6.9mmo/l	8	14,668	10.7	7.7-14.8		306.42 (7)*	97.7
3) FPG 6.1-6.9 and 2hPG <7.8mmo/l	4	3,999	9.7	6.4-14.3		52.87 (3)*	94.3
Quality Category							
1 – Higher	6	6,685	10.6	8.7-12.8	0.09 (2)	30.24 (5)*	83.5
2	5	8,523	10.9	7.5-15.4		129.52 (4)*	96.9
3 – Lower	4	6,205	9.4	3.7-21.8		298.73 (3)*	99
Country							
Finland	2	2,320	11.6	8.6-15.3	136.74 (8)*	6.39 (1)*	84.4
France	3	6,177	7.5	3.6-14.9		111.53 (2)*	98.2
Germany	1	896	4.2	3.1-5.7		0.00 (0)	0.0
Greece	1	1,514	20.5	18.5-22.6		0.00 (0)	0.0
Italy	1	2,240	12.2	10.9-13.6		0.00 (0)	0.0
Netherlands	1	2,378	12	10.8-13.4		0.00 (0)	0.0
Spain	2	752	6.1	1.9-18.4		15.4 (1)*	93.5
Sweden	1	359	10.6	7.8-14.2		0.00 (0)	0.0
UK	3	4,777	14.4	11-18.8		14.64 (2)*	86.3

Variable	k	N	Prevalence	95% CI	Q_B (df)	Q_W (df)	I^2 (%)
			Women				
Age							
18 and over	6	6,685	6.5	4.4-9.7	0.96 (2)	91.2 (5)*	94.5
30-65	6	6,169	5.2	3.9-6.8		31.32 (5)*	84
66+	2	9,287	7.3	1.1-35.9		477.71 (1)*	99.8
Diagnostic Criteria							
1) FPG 5.6-6.9mmol/l	7	14,610	7.2	3.9-13	1.27 (2)	549.58 (6)*	98.9
2) FPG 6.1-6.9mmo/l	2	2,846	6.5	1.8-20.8		62.61 (1)*	98.4
3) FPG 6.1-6.9 and 2hPG <7.8mmo/l	4	4,103	4.7	3.0-7.4		30.93 (3)*	90.3
Quality Category							
1 – Higher	5	4,977	5.9	3.9-9.1	0.06 (2)	47.09 (4)*	91.5
2	5	8,298	6.3	3.0-12.7		287.22 (4)*	98.6
3 – Lower	4	8,866	5.5	2.3-12.4		206.1 (3)*	98.5
Country							
Finland	2	2,595	5.1	4.3-6	119.82 (7)*	0.12 (1)	0.0
France	3	8,647	3.8	2.4-5.9		29.57 (2)*	93.2
Germany	1	757	1.9	1.1-3.2		0.00 (0)	0.0
Greece	1	1,528	12	10.5-13.7		0.00 (0)	0.0
Italy	1	2,497	9.9	8.8-11.1		0.00 (0)	0.0
Spain	2	967	4.7	1.9-11.3		9.46 (1)*	89.4
Sweden	1	382	6.3	4.3-9.2		0.00 (0)	0.0
UK	3	4,771	10.6	5.6-19.2		56.12 (2)*	96.4

* $p<0.05$; 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

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).

Analysis of moderators for combined impaired glucose tolerance and impaired fasting glucose

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 6 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).

Table 6: Mean prevalence of combined IGT and IFG by several moderator variables

Variable	k	N	Prevalence	95% CI	Q_B (df)	Q_W (df)	I^2 (%)
Age							
18 and over	4	9,959	3.5	2.5-4.7	7.94 (2)*	21.53 (3)*	86.1
30-65	6	14,605	1.9	1.5-2.5		24.88 (5)*	79.9
66+	1	499	2.7	1.6-4.6		0.00 (0)	0.0
Quality Category							
1 – Higher	2	6,077	3.2	1.7-6	1.63 (2)	12.5 (1)*	92
2	3	5,908	1.8	1-3.4		21.95 (2)*	90.9
3 – Lower	6	13,080	2.6	1.9-3.6		42.26 (5)*	88.2
Country							
Finland	2	3,217	1.9	1.1-3.4	15.12 (5)*	3.56 (1)*	71.9
Germany	1	1,653	1.2	0.8-1.9		0.00 (0)	0.0
Italy	1	919	2.1	1.3-3.3		0.00 (0)	0.0
Portugal	1	5,167	2.4	2-2.9		0.00 (0)	0.0
Spain	4	7,882	3.4	2.5-4.7		19.79 (3)*	84.8
UK	2	6,225	2.4	1.2-4.5		14.2 (1)*	93

* $p<0.05$; 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.

Multivariate 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 7 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.

Table 7: Weighted multiple regression for combined IGT and IFG prevalence

	β	95% CI	$Q_{(B)}$ (df)
Age			
18 +	0.61	-0.08-1.3	4.47 (2)
30-65	-	-	-
66+	0.6	-0.39-1.59	
Country			
Finland	0.23	-0.71-1.17	5.97 (5)
Germany	-	-	-
Italy	0.57	-0.42-1.56	
Portugal	0.1	-1.04-1.23	
Spain	0.62	-0.3-1.54	
UK	0.42	-0.13-1.5	

*p<0.05

3.5 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 (DECODE study group 2003). 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 (Joanna Briggs Institute, 2014). 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 (DECODE Study Group 2003; Qiao et al. 2000; DECODA Study Group 2003; DECODE Study Group 2002). 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 diabetes and sharing the same risk factors, we would expect to see increases in IGR over time mirroring those seen for type 2 diabetes (Nathan et al. 2007). 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 (Gardete-Correia et al. 2010). 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 diabetes. 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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3.6 Critical reflection

Critique of methods

This systematic review and meta-analysis has a number of strengths including the fact that independent reviewers were used to screen all of the titles and abstracts identified by the search, decisions about inclusion were discussed and agreed upon by three authors, a thorough quality assessment was conducted for all studies and the majority of studies included were of high quality. However, the limited time and resources available for conducting this review meant that experts in the field were not contacted, grey literature

was not identified, only papers published in the English language were included, independent screening was split between two authors and data extraction was only carried out by one author. A further weakness of the study related to the approach taken to assessing study quality. These limitations will now be discussed in more depth.

The purpose of a systematic review is to attempt to identify all of the relevant evidence that is available on a given topic. Not contacting experts in the field or identifying grey literature potentially limits the ability of this systematic review to do this. Including grey literature in systematic reviews can help to minimise the effects of publication bias (Paez 2017). Publication bias is the tendency for significant positive results to be published, published earlier, published in English, and published in journals with higher impact factors than nonsignificant results (Sterne et al. 2001). Therefore, by not including grey literature the findings of this systematic review may be biased. However, the CRD (2009) guidance recognises that contacting experts in the field in order to identify unpublished literature is time consuming and offers no guarantee of obtaining relevant information. Hartling et al. (2017) reviewed 129 systematic reviews on three topics and found that although most reviews searched for unpublished studies, very few included these studies with unpublished studies representing less than 2% of included studies. In the majority of cases inclusion of unpublished studies had negligible or small impact on the results (Hartling et al. 2017). On balance, in the present systematic review it was felt that time and resources could be better used in other areas of the review process.

Excluding articles published in languages other than English may have also biased the findings of the review. Research has shown that studies with statistically significant results conducted in non-English speaking countries are more likely to be published in English language journals than those with non-significant findings, a phenomenon known as language bias (Egger et al. 1997). However, research investigating the impact of this bias on the findings of systematic reviews is conflicting. For example, a paper exploring the effects of limiting meta-analyses by language reported that estimates of intervention effectiveness did not differ according to whether the meta-analysis restricted studies by language (Moher et al. 2000). However, Moher et al. (2000) did find that language restricted meta-analyses had significantly lower precision than those that included papers in any language because the analyses were based on fewer data. In contrast to the Moher et al. (2000) study, Jüni et al (2002) found that non-English trials were more likely to

have significant results and higher effect sizes. A systematic review of empirical studies assessing the effect of English language restriction concluded that there was no evidence of a systematic bias from the use of language restriction in systematic reviews in conventional medicine (Morrison et al 2012). Although these findings suggest that there is no evidence that restricting inclusion by language affects estimates, all of the research discussed looked at randomised controlled trials of effectiveness of interventions and therefore may not be generalizable to the present meta-analysis which included different study types.

The CRD (2009) and Cochrane guidance (Sterne et al. 2011) recognise that it is not always possible to include papers in languages other than English due to lack of time, facilities and resources. The CRD (2009) guidance recommends that in this case, non-English language papers should be identified, documented and noted as being excluded on the basis of language. In line with this recommendation, the authors of the present meta-analysis checked and recorded non-English articles during the screening process. English abstracts were available for all studies and from these abstracts a total of five non-English language articles were identified as potentially relevant. Four of the five papers reported IGT prevalence and one reported both IGT and IFG prevalence suggesting that the precision of the estimate for IGT may have been affected by the exclusion of non-English language articles. However, these five studies together included 4,644 participants which represents only 6% of the total number of participants included in the meta-analysis suggesting they are unlikely to have had a large effect on either pooled estimates or the precision of these.

Several well-established handbooks for conducting systematic reviews recommend that at least two authors independently screen the records identified by the search (Higgins and Deeks 2011; CRD 2009; Eden et al. 2011). In the present review, the independent screening was split between two authors due to these authors having limited time to spend on the review. This involved the first author screening all records and the second author independently screening half and the third author independently screening the remaining half. Having two independent reviewers screening papers, rather than one, may have increased the variability in the screening process which could have resulted in papers being missed. Conversely, it could be argued that having two independent reviewers could be advantageous if it reduces the risk of reviewers becoming fatigued and making

errors. It would have been valuable to calculate agreement scores to assess if there were any differences in the way the two independent reviewers conducted screening compared to the first author. The CRD guidance on conducting systematic reviews states that reliability of the decision-making process is increased if all papers are independently assessed by more than one researcher. A study by Edwards et al. (2002) assessed the accuracy and reliability of reviewers when screening records for systematic reviews and found that a single researcher misses on average 8% of eligible papers whereas a pair of reviewers did not miss any. While the approach taken in this systematic review was not ideal, this research suggests that it was likely to have resulted in fewer missed eligible studies than if the first author had reviewed the papers alone.

Data extraction is a process that requires subjective judgements to be made about how to record variables of interest. Having only one author carry out data extraction, as was the case in publication one, increases the risk of errors in a systematic review. Research has shown that data extraction by a single researcher results in around 53% more errors of inaccuracy (where reporting of a given item was incorrect) and around 7% more errors of omission (information for a variable was missing or incomplete) than when conducted independently by two researchers (Buscemi et al. 2006). However, only the finding of increased inaccuracy errors was statistically significant. Buscemi et al. (2006) also found significant differences in the time spent on a single paper when data extraction was carried out by two researchers. The time spent on a single data extraction was 36% less when there was only one researcher conducting data extraction compared to a single data extraction when there are two researchers involved in the process. The authors of this study conclude that the decision to employ single or double data extraction will depend upon the time and human resources available for the review.

The CRD (2009) guidance suggests that when resources are limited a second author can check the data extraction forms for accuracy and completeness. This method is likely to result in more errors than having two researchers' independently complete data extraction but takes less time. Data extraction forms were not checked for accuracy in publication one due to limited resources. On reflection, having a second author check accuracy would have been an option for reducing errors in the present meta-analysis without incurring excessive time costs. The research by Buscemi et al. (2006) suggests that the decision to not carry out double data extraction or checking of data extraction is likely to have

resulted in their being more errors of inaccuracy in the present meta-analysis. Error of inaccuracy relating to the extraction of prevalence figures and demographic variables could have affected the mean figures for prevalence reported in the study. However, given that there were a large number of studies included in the meta-analysis it is less likely that errors of inaccuracy would have had a big effect on mean prevalence figures. Although double data extraction can reduce errors, the research by Buscemi et al. (2006) shows that it does not eliminate them completely.

The way that quality was assessed and reported in the published report of this systematic review and meta-analysis has potentially conflated issues with study quality, risk of bias or reporting quality. Studies with these different types of quality issues were combined together in to groups categorised as low medium or high quality and this category was reported for each study. A more appropriate approach would have been to report the specific quality issues for each study in the table describing the studies.

Critique of analysis

When used appropriately, there are several strengths of meta-analysis as a tool for summarising findings from a systematic review. A key strength of meta-analysis is that it allows the findings to be presented in a more sophisticated way than can be achieved by a qualitative summary or by counting the number of statistically significant results. Statistical significance is heavily influenced by sample size and as a result studies may report a meaningful effect that is not statistically significant because of small sample size and low power (Lipsey and Wilson 2000). By pooling the size and direction of effects across a range of studies, meta-analyses can have increased power to detect relationships and increased precision in estimates. It also offers the opportunity to answer questions that are not posed by individual studies and can also allow exploration of differences between studies and their findings that can be difficult to decipher in a narrative analysis (Deeks et al. 2011).

Although meta-analysis can be a powerful tool, there are situations where is it not possible or advisable to use this method of analysis. A common criticism of meta-analyses is that they sometimes attempt to ‘combine apples and oranges’: meaning that they combine studies with diverse methods and outcomes. It is argued that summary statistics produced by meta-analyses are meaningless if they aggregate diverse studies

(Deeks et al. 2011). Decisions around which studies should and should not be combined are subjective and require discussion among researchers. In the present meta-analysis, these issues were discussed early in the review process. As a result of these discussions the authors restricted the meta-analysis to include only studies assessing IGR using FPG or 2hPG and excluded those using HbA1c to ensure that studies were using comparable outcomes. This resulted in a set of studies in the present meta-analysis with a relatively narrowly defined outcome of interest. However, despite efforts to reduce heterogeneity in measurement of outcomes there were differences in sampling methods from study to study. Another potential weakness of meta-analysis arises when studies at high risk of bias are included. Meta-analyses that include studies with a high risk of bias produce results that are potentially seriously misleading as meta-analysis compounds any errors in included studies (Deeks et al. 2011). This risk was minimised in the present meta-analysis by the exclusion of studies that were believed to be at high risk of bias.

A final weakness of this paper, and of the other quantitative papers in this thesis, relates to the imprecise use of the term rate. The term rate refers to the frequency with which an event occurs in a population over a defined period of time (Webb and Bain 2011). There are several references to prevalence as a rate in the quantitative publications in this thesis which is incorrect as prevalence is a proportion and has no element of time.

Chapter four: Prevalence of gestational diabetes mellitus in Europe (publication two)

Eades, C.E., Cameron, D. and Evans, J.M.M. (2017) Prevalence of gestational diabetes mellitus in Europe: a meta-analysis. *Diabetes Research and Clinical Practice*, 129, pp. 173-181.

This paper was published in Diabetes Research and Clinical Practice, a peer reviewed journal with an impact factor of 3.64, and has been cited 27 times. It is an international journal that publishes research on diabetes and related areas aimed at health care providers and clinically orientated researchers and is the official journal of the International Diabetes Federation.

The content of the above publication is presented in this chapter followed by a section providing critical reflection of the methods. A PDF of the published manuscript can be found in appendix 5.

A verbatim copy of publication two starts below.

4.1 Abstract

Aims: Estimates of the prevalence of gestational diabetes mellitus (GDM) vary widely. It is important to have a clear understanding of the prevalence of this condition to be able to plan interventions and health care provision. This publication describes a meta-analysis of primary research data reporting the prevalence of GDM in the general pregnant population of developed countries in Europe.

Methods: Four electronic databases were systematically searched in May 2016. English language articles reporting GDM prevalence using universal screening in general pregnant population samples from developed countries in Europe were included. All papers identified by the search were screened by one author, and then half screened independently by a second author and half by a third author. Data were extracted by one author. 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 3258 abstracts were screened, with 40 studies included in the review. Overall prevalence of GDM was 5.4% (3.8-7.8). Maternal age, year of data collection, country, area of Europe, week of gestation at testing, and diagnostic criteria were found to have a significant univariate effect on GDM prevalence, and area, week of gestation at testing and year of data collection remained statistically significant in multivariate analysis. Quality category was significant in multivariate but not univariate analysis.

Conclusions: This meta-analysis shows prevalence of GDM that is at the upper end of previous estimates in Europe.

4.2 Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is first diagnosed in pregnancy and increases the risk of complications for both mother and baby during pregnancy (Buckley et al. 2012). It is estimated that GDM affects around 7% of all pregnancies worldwide although prevalence is difficult to estimate as rates vary from study to study because of a lack of accepted diagnostic criteria and differences in screening procedures (American Diabetes Association [ADA] 2003). Some earlier diagnostic criteria were based on the criteria used in non-pregnant individuals and in others thresholds were created based on the predictive value of future type 2 diabetes in the mother. In recent years, there has been an increasing focus on diagnostic thresholds that predict the likelihood of adverse outcomes in pregnancy (HAPO; Hadar et al. 2009). Adverse outcomes include macrosomia, shoulder dystocia and birth injury, primary caesarean delivery, preeclampsia, preterm delivery and foetal and neonatal mortality (Yogev and Visser 2009).

In addition to adverse outcomes during pregnancy and birth, the consequences of GDM extend beyond pregnancy with affected women having a seven fold increased risk of type 2 diabetes compared to women who have not had GDM. Rates of type 2 diabetes after a diagnosis of GDM vary depending on the population and length of follow up, but have been reported to be as high as 70% (Ferrara 2007; Kim et al. 2002). Women are thought to be at the greatest risk of developing type 2 diabetes in the first five years following a pregnancy with GDM, with incidence of type 2 diabetes plateauing at around 10 years (Kim et al. 2002).

Although women who have had GDM are at an increased risk of type 2 diabetes, research has shown that by making lifestyle changes they can prevent or delay progression to type 2 diabetes (Unwin et al. 2002). With prevalence of type 2 diabetes increasing rapidly, a diagnosis of GDM represents an opportunity for intervention to reduce the burden of type 2 diabetes (Davies et al. 2004). This is why it is so 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. We have therefore conducted a meta-analysis of observational primary research studies that have assessed the prevalence of GDM in the general population of pregnant women in developed countries in Europe, regardless of the specific diagnostic criteria used. We have derived an overall prevalence estimate for GDM and examined moderator variables that potentially influenced this estimate. Although narrative reviews exist on this topic, this is the first systematic review and meta-analysis to bring together and synthesise all the evidence.

4.3 Material and methods

Literature search and study selection

A meta-analysis of primary research studies reporting prevalence of GDM was undertaken in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reviews (Stroup et al. 2000). A search was conducted in MEDLINE, CINAHL, Health Source and PsycInfo for articles published before June 2016. The following combination of search terms were used with each database: (prevalence or incidence) and (gestational diabetes or diabetes in pregnancy or gestational diabetes mellitus). Reference lists and citations of included papers were checked to identify any other potentially relevant papers but key authors and experts 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 all papers were screened by one author (CE). Independent screening of records was split between the two other authors, with JE screening half and DC screening the other half. The full texts of papers were retrieved for studies that were considered relevant, but also for those that contained insufficient information to allow judgement of relevance. These were checked against the inclusion criteria by CE and independently by JE. Reference lists of included articles were reviewed to identify any additional relevant articles. 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.

Papers were screened against the following inclusion criteria:

Population: general population of pregnant women, living in a developed country in Europe (as defined by the Financial Times Stock Exchange).

Outcome measure: prevalence of GDM diagnosed using universal screening carried out in the second or third trimester, using either a glucose tolerance test (GTT) alone or two step screening with glucose challenge test (GCT) followed by a GTT.

Study design: observational study, published in English.

The review was limited to developed countries in Europe because of the wide differences in prevalence of type 2 diabetes and GDM between developed and developing countries (Ferrara 2007; Wild et al. 2004). This removed one potential source of heterogeneity in the review and also ensured its relevance 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 of pregnant women if it was drawn from a source that covered the majority of the population, such as population registers, general practice registers or registers of clinics for pregnant women (in countries where registration at general practices and clinics for pregnancy women 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 GDM (due to family history of type 2 diabetes, or lifestyle and medical factors) were excluded. Studies were excluded if the majority of the sample were immigrants and did not originate from an included developed country.

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 (CRD 2009). 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, type of screening/testing carried out and diagnostic criteria for GDM. The outcome measures extracted were number and proportion of sample with GDM, and where reported the number and proportion of sample with GDM by different demographic factors such as age and Body Mass Index (BMI).

Where individual studies reported multiple prevalence estimates according to different diagnostic criteria, only one prevalence estimate was included in the meta-analysis to avoid dependency effects. The prevalence estimate deriving from the criteria that were most commonly used in other papers in the review was the one selected for inclusion in the meta-analysis so that the estimate would be 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 (2014) 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 high, medium or low according to how likely they were to put the study at risk of bias. High risk weaknesses were those that put the study at high risk of bias or made the risk of bias difficult to assess, and 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 GDM. Medium risk weaknesses included low participation rate (50-70%), not reporting women's gestation at testing and sample size of less than 300. Low risk

weaknesses included not reporting characteristics of the sample and not reporting differences between participants and non-participants.

Included studies were then given a quality rating as follows:

1: Only low risk weaknesses

2: One medium or more than one low risk weakness.

3: One high risk or multiple medium risk weaknesses.

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 GDM was transformed into a logit event rate effect size and the standard error associated with this was calculated (Lipsey and Wilson 2000). The logits were retransformed to proportions after analysis to aid interpretation of the results. Combined effect sizes were calculated and analyses were carried out twice: both including and excluding outlying logit event rates. No significant differences were found between these analyses 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 (Lipsey and Wilson 2000). In contrast, random effects models allow for the possibility that there are also random differences between studies that are not only due to sampling error but as a result of some other factor such as variation in procedures, measures or settings. The choice of the random effects model to combine studies in this meta-analysis was based upon literature on GDM prevalence which suggests that the variability in reported prevalence for GDM may be the result of the use of different methodologies and criteria (Ferrara 2007).

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.

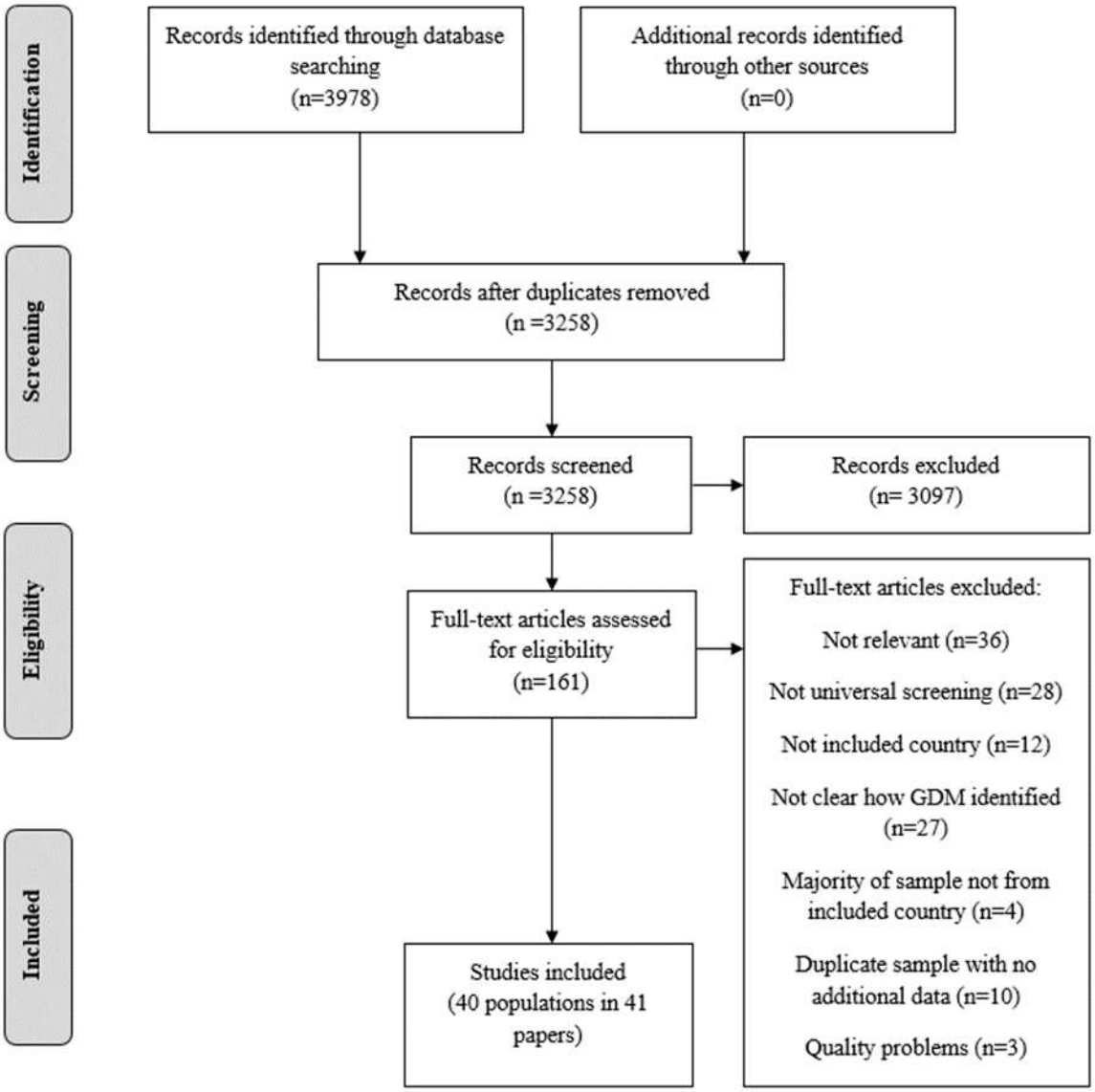
4.4 Results

Description of included studies

Figure 2 shows a PRISMA flow diagram of studies identified by the search. The search identified 3,258 abstracts of which 161 were potentially relevant after title and abstract screening. The full text articles were retrieved and assessed against the inclusion criteria, resulting in 40 included studies reported in 41 papers (Aberg et al. 2001; Alberico et al. 2004; Anderberg et al. 2007; Avalos et al. 2013; Breschi et al. 1993; Bugallo et al. 2011; Cauza et al. 2005; Chevalier et al. 2011; Chico et al. 2005; Coolen and Verhaeghe 2010; Cordero and et al. 2015; Corrado et al. 2012; Cosson et al. 2006; Di Cianni et al. 2003; Duran, et al. 2014; Fadl et al. 2010; Fedele and Lapolla 1997; Griffin et al. 2000; Ignell et al. 2014; Janghorbani et al. 2006; Jimenez-Moleon et al. 2002; Lacaria et al. 2015; Lind and Anderson 1984; Lindqvist et al. 2014; Malmqvist et al. 2013; Meek et al. 2015; Miailhe et al. 2015; Orecchio et al. 2014; Ostlund and Hanson 2003; Perez-Ferre et al. 2012; Pintausdi et al. 2013; Poyhonen-Alho et al. 2005; Ricart et al. 2005; Ruetschi et al. 2016; Sommer et al. 2015; Vassilaki et al. 2015; Vignoles et al. 2011; Sacks et al. 2012; Murgia et al. 2008; O'Sullivan et al. 2011; Oriot et al. 2014). These 40 studies included a total of 1,778,399 participants. The characteristics of the studies included in the review are presented in Table 8 (Appendix 4). Studies were conducted across 11 of the 17 countries defined as developed European countries: Italy (n=9), Sweden (n=7), Spain (n=7), France (n=4), UK (n=5), Ireland (n=2), Belgium (n=2), Greece (n=1), Finland

(n=1), Austria (n=1), and Switzerland (n=1). No additional papers were identified by manual searching of reference lists.

Figure 2: Flow diagram showing study selection



Around half of studies (n=22) used a single step screening strategy where all women were given a GTT, and the others used two-step screening, where all women were screened first with a GCT, then those with a positive GCT were given a GTT. Two studies used both one-step screening in one cohort, and two-step screening in a second separate cohort

of women (Duran et al. 2014; O'Sullivan et al. 2011). The most commonly used diagnostic criteria were Carpenter and Coustan (1982) which were used to diagnose GDM in 14 studies as part of two-step screening and one study using one-step screening. The International Association of Diabetes and Pregnancy Study Group criteria (IADPSG 2010) were applied in a total of ten studies, of which nine used one-step screening and one used two-step screening. The National Diabetes Data Group (NDDG 1979) criteria were used in three studies using two-step screening and one study using one-step screening. A modification of the European Association for the Study of Diabetes (1988; EASD) criteria that diagnosed GDM on the basis of two hour values only without assessing fasting blood glucose was used in four studies all using one step screening. Only three studies reported that they tested for and excluded any women with undiagnosed pre-existing diabetes that was uncovered in the first trimester.

Quality of studies

The quality category assigned to each study is reported in Table 8 (Appendix 4). Three studies were identified that had two major weaknesses (Di Cianni et al. 1997; Mello et al. 1997; Vitoratos et al. 1997): in all three studies it was not clear if the study sample was a whole population of pregnant women and response rates were not reported. 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. The majority of included studies were classed as either the higher (n=23) or middle quality category (n=11) and therefore had only low or medium risk weaknesses. The remaining studies fell in to the lower quality category (n=6) and in addition to any low risk weaknesses also had weaknesses that put the study at higher risk of bias. These higher risk weaknesses included non-reporting of response rate (n=4), not reporting where women were recruited from (n=1) and very low participation rate (n=1). Of the weaknesses categorised as low or medium risk, the most common problems were non-reporting of sample characteristics (n=21), non-reporting of information on women who did not participate (n=17), low participation rate (n=5), and non-reporting of gestation at testing (n=2).

Analysis of outliers

One outlier was identified that reported prevalence of 35.5% (Duran et al. 2014). This figure was reported for a cohort of women with a median age of 32 and median pre-pregnancy BMI of 22.8kg/m^2 and who were diagnosed with GDM through universal

screening using IADSPG criteria. The majority of women were Caucasian (62%) and only 2% had previous GDM. These characteristics are largely similar to those of other studies giving no clear explanation for the high prevalence found in this study.

Mean prevalence of gestational diabetes mellitus

The mean prevalence of GDM overall was 5.4% (95% CI: 3.8-7.8). The mean prevalence in studies using one-step screening was 6.4% (3.8-10.4) and 4.7% (2.7-8.1) in studies using two-step screening. There was no significant difference in prevalence of GDM between studies using one-step and two-step screening ($Q_{[1]}$=0.64; p=0.424). The analysis of homogeneity in the data with regards to type of screening showed variability within studies assessing prevalence using one-step screening ($Q_{[19]}$=13019.04; p<0.001) and those using two-step screening ($Q_{[21]}$=15517.54; p<0.001).

Analysis of moderators for GDM

As there was no significant difference in prevalence of GDM by screening type, the analysis of prevalence by moderator variables is presented in overall terms. Table 9 shows the individual effects of different categorical moderator variables. Sample age, diagnostic criteria, country the study was conducted in, year that data collection started and week of gestation at testing, all had a significant effect on the prevalence of GDM, whereas the quality category of studies, mean BMI, ethnicity, and family history of diabetes in samples, did not have a significant effect. There were too few studies reporting parity data for this variable to be included in analyses.

Sample age

Prevalence was higher in samples with a mean age of 30.8 years and over (9.6%; 6.7-13.7) compared to those with a mean age of 30.7 and under (4.3%; 2.3-8.0).

Diagnostic criteria

Analysis of the effect of diagnostic criteria on GDM prevalence found the highest prevalence estimate in studies using the IADPSG criteria (14.1%; 9-21.5; 2010), the second highest prevalence was found in studies using Carpenter and Coustan criteria (6.9%; 5.4-8.7; 1982). The second lowest prevalence estimate was in studies using the NDDG criteria (5.3%; 2.7-10; 1979) and the lowest estimate was for those that defined GDM using modified EASD criteria with two hour readings only (1.4%; 0.9-2.2; 1988).

Table 9: Mean prevalence of GDM by several moderator variables

Variable	k	N	Prevalence	95% CI	Q_B [df]	Q_W [df]	I^2 [%]
Mean age [years]							
30.7 and below	9	122,648	4.3%	2.3-8.0	4.75 [1]*	2312.38 [8]*	99.7
30.8 and above	9	43,327	9.6%	6.7-13.7		806.49 [8]*	99
Diagnostic Criteria							
NDDG	4	11,927	5.3%	2.7-10	60.1[3]*	79.13 [3]*	96.2
Carpenter Coustan	15	47,502	6.9%	5.4-8.7		621.28 [14]*	97.7
EASD 2 hour only	4	299,153	1.4%	0.9-2.2		420.48 [3]*	99.3
IADPSG	10	46,557	14.1%	8.9-21.5		2275.49[9]*	99.6
Quality Category							
1 – Higher	24	325,888	6.0%	4.1-8.5	3.0 [2]	7999.56 [21]*	99.7
2	12	1,442,4833	3.9%	2.2-7.1		6869.37 [11]*	99.8
3 – Lower	6	13,895	7.6%	4.8-12.0		366.60 [5]*	98.6
Country							
Austria	1	2,421	8.6%	7.5-9.8	101.96 [10]*	0.00 [0]	0.0
Belgium	3	2,497	9%	3.3-22.2		133.24 [2]*	98.5
Finland	1	532	2.8%	1.7-4.6		0.00 [0]	0.0
France	4	19,080	8%	4.1-14.9		403.18 [3]*	99.26
Greece	1	1,122	9.1%	7.5-10.9		0.00 [0]	0.0
Ireland	2	6,799	5.9%	1.3-23.8		85.59 [1] *	9.8
Italy	9	13,486	10%	7.6-13		210.45 [8]*	96.2
Spain	8	34,031	8.6%	5.1-14.1		1259.12 [7]*	99.4
Sweden	7	1,663,514	1.5%	1-2.3		3335.68 [6]*	99.8
Switzerland	1	1042	4.8%	3.7-6.3		0.00 [0]	0.0
UK	5	37,292	2.4%	0.8-7.0		1519.62 [4] *	99.7

Variable	k	N	Prevalence	95% CI	Q_B [df]	Q_W [df]	I^2 [%]
Area of Europe							
Northern	15	1,708,137	2.3%	1.3-3.8	24.32 [2] *	14880.94[14]*	99.9
Western	9	26,346	7.3%	4.6-11.3		651.79 [8]*	98.8
Southern	18	47,783	9.6%	7.3-12.6		1530.48 [17] *	98.9
Year data collection started							
1980-1989	2	2,824	0.9%	0.1-10	14.95 [3] *	27.77 [1] *	96.4
1990-1999	14	1,508,604	2.9%	1.9-4.5		5500.94 [13] *	99.8
2000-2009	13	233,199	6.9%	4.3-10.8		5434.77 [12] *	99.8
2010-2016	9	34,343	11.1%	5.7-20.6		2187.66 [8] *	99.6
% sample with family history of diabetes							
14% and below	5	10,106	12%	5.2-25.3	0.971 [1]	804.53 [4] *	99.5
15% and over	3	9,989	7.6%	4.9-11.5		65.3 [2] *	96.9
% sample Caucasian							
79% and below	2	3,276	20.3%	5.4-53.6	2.73 [1]	265.93 [1] *	99.6
80% and over	7	102,821	5.5%	2.4-12.3		3040.83 [6] *	99.8
Gestation at testing							
24-28 weeks	28	105,096	7.5%	5.9-9.4	104.85 [3] *	2841.69 [27] *	99.1
28 weeks	6	381,273	1.9%	1.5-2.5		449.79 [5] *	98.9
28-32 weeks	1	3,616	1.7%	1.3-2.2		0.00 [0]	0.0
Multiple time points	4	8,877	13.1%	6.5-24.7		367.84 [3] *	99.2
Mean BMI							
20-24.9	10	19,131	9.8%	5.5-16.9	0.39 [1]	1062.55 [7] *	99.3
25-29.9	2	6,799	5.9%	1.3-23.8		85.59 [1] *	98.8

* $p<0.05$; 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.

Country

In the analysis by country, the highest prevalence was found in studies conducted in Italy (10%; 7.6-13) and the lowest in Sweden (1.5%; 1-2.3). Countries were sorted into three groups according to location in Europe: Northern Europe, Western Europe, Southern Europe. Highest prevalence was found in countries in Southern Europe (9.6%; 7.3-12.6) and lowest in Northern Europe (2.3%; 1.3-3.8).

Year

Estimates of GDM prevalence increased every decade with the lowest in the 1980s [0.9%; 0.1-10] and the highest in the 2010s (11.1%; 5.7-20.6).

Gestation at testing

The highest prevalence estimate for GDM was found in studies that screened for GDM at multiple time points in the second and third trimester (13.1%; 6.5-24.7) followed by those studies that tested participants between 24 and 28 weeks of gestation (7.5%; 5.9-9.4) . The lowest prevalence estimate was in a study that screened for GDM at 28 to 32 weeks gestation (1.7%; 1.3-2.2). However, as this category only contained a single study this result must be interpreted with caution. The second lowest prevalence estimate was found in studies that screened only at 28 weeks of gestation (1.9%; 1.5-2.5).

Multivariate analysis

A weighted multiple regression was performed in order to explore which variables made the greatest contribution to the variability in prevalence of GDM. All variables explored in the univariate analysis were initially entered into the model except for sample age and mean BMI as there were too few studies reporting these variables for them to be included in the multivariate analysis. Correlations between different variables were explored and used to inform the selection of variables for the multiple regression. A moderate correlation was found between year of data collection and diagnostic criteria ($r=0.478$; $p=0.010$; $n=28$). The variable diagnostic criteria could not be included in the multiple regression because of collinearity with this and other variables.

The final model included the following variables: quality category, type of screening (one or two step), gestation at testing, year data collection started and area of Europe. These variables accounted for 83% of total observed variability ($Q_{R[11]}=125.6$, $p<0.001$, see

Table 10 for full results). All three of the variables that were significant in univariate analyses (area, gestation at testing and year of data collection) remained statistically significant when the other variables were held constant. Quality category and type of screening were not significant in univariate analysis but were significant in the multiple regression. However, the residual model was also statistically significant ($Q_{E[23]}$=1134.95; p<0.001, I^2=98.0%) meaning that there was still variability in the data that was not explained by the variables analysed.

Table 10 Weighted multiple regression for GDM prevalence

	β	**95% CI**	**$Q_{[B]}$ [df]**
Quality Category			
1 – Higher	-	-	14.85 [2] *
2	0.042	-0.35-0.44	
3 – Lower	0.97*	0.47-1.47	
Area of Europe			
North	-	-	18.07 [2] *
West	0.54*	0.02-1.06	
South	1.04*	0.54-1.53	
Year data collection started			
1980-1989	-	-	29.03 [3] *
1990-1999	1.85*	0.71-3.0	
2000-2009	2.37*	1.21-3.52	
2010-2016	2.74*	1.61-3.88	
Gestation at testing			
24-28 weeks	0.49	-0.54-1.52	9.58 [3]*
28 weeks	-0.15	-1.11-0.83	
28-32 weeks	-	-	
Multiple time points	1.03	-0.11-2.17	
Type of Screening			
One step	-	-	
Two step	-0.41*	-0.77—0.04	

* p<0.05; Q_B: between study homogeneity statistic

4.5 Discussion

This meta-analysis of 1,770,63 participants in 40 studies reported mean prevalence of GDM of 5.4%. No differences were found in prevalence estimates of GDM according to the type of screening used (one-step or two-step), mean BMI, ethnicity and family history. An increase in prevalence was found with increasing sample age and year of data collection. Diagnostic criteria, country and week of gestation at testing were also found to have an effect on GDM prevalence. Nevertheless, given the changing migration patterns across Europe, this prevalence estimate may well change in the future.

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 with coverage of the majority of the pregnant population (e.g. clinic register) using appropriate methods (e.g. whole population). The majority of included studies had good participation rates. Only four studies had participation rates of 50 to 70% and only one study had a very low participation rate of less than 50%. This allows us to be reasonably confident that the included studies used samples that were representative of the general pregnant population. Quality category of the study was not found to have any significant effect on prevalence of GDM in univariate analysis but was significant in the multiple regression.

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 GDM

prevalence was also made difficult by heterogeneity in approaches to sampling, methods used to collect blood samples and the criteria used to define GDM.

The way GDM is defined makes it difficult to differentiate between pre-existing undiagnosed diabetes and GDM. The IADPSG guidelines suggest that all women or those at high risk have either fasting blood glucose, A1c or random blood glucose measured at the first prenatal visit and overt diabetes diagnosed if fasting blood glucose is 126mg/dl or higher or A1c 6.5% or higher (IADPSG 2010). Only three of the studies included in the present review reported that they tested for pre-existing undiagnosed diabetes in this way and excluded any women meeting the criteria. Of these three studies two reported the number of women thus identified and in both the prevalence was very low at 0.1% and 0.5%. Similarly, analysis of the national health and nutrition examination survey carried out between 1999 and 2010 in the United States showed that approximately 0.5% of women of non-pregnant women of reproductive age had undiagnosed diabetes (Razzaghiet al. 2015). Therefore, although estimates of GDM may be inflated by the potential inclusion of women with undiagnosed pre-existing diabetes, given the low prevalence of this it is unlikely that the effect on GDM estimates would be large.

The ADA guidelines estimate that around 7% of pregnant women will be diagnosed with GDM (ADA 2003) and a review by of GDM prevalence in Europe reported rates of between 2 and 6% (Buckley et al. 2012). This estimate of 2-6% was based on studies using both risk-based and universal screening, whereas our estimate of 5% was based only upon studies using universal screening which identifies more women with GDM than risk-based screening (Anderberg et al. 2007; Ostlund and Hansen 2003).

The specific diagnostic criteria was found to have a significant effect on prevalence estimates in this review, with the IADPSG (2010) criteria giving the highest estimates and a modified EASD (1988) and Carpenter Coustan (1982) giving the lowest estimates. In contrast, the review by Buckley et al. (2012) reported no consistent trend in prevalence according to diagnostic criteria. The IADPSG criteria were proposed on the basis of evidence from the HAPO study on the relationship between maternal hyperglycaemia and adverse outcomes. A number of associations, including the ADA, have adopted these recommendations while others have argued that they will increase prevalence without necessarily improving outcomes. A study by Duran et al. (2014) has since shown that while using the IADPSG criteria does increases GDM prevalence, it also results in

significant improvements in pregnancy outcomes. This study reported increases in prevalence of 3.5 times compared to Carpenter and Coustan criteria whereas we found rates according to IADPSG criteria to be around double Carpenter and Coustan.

The present review confirmed previous research showing that GDM prevalence increases with increasing maternal age and is higher in Southern and Western Europe compared to Northern Europe (Buckley et al. 2012). We did not find any effect for BMI, ethnicity or family history, but there were few studies that measured or reported these variables so there may have been insufficient power to detect any differences. A strength of the present study is that pooling studies using meta-analysis allows trends to be identified when there are inconsistencies between individual studies.

With GDM being closely linked to type 2 diabetes and sharing some risk factors, we would expect to see an increase in GDM over time (Buckley et al., 2012). Although we found significant increases in GDM prevalence over time, year of data collection was moderately correlated with diagnostic criteria. The IADPSG criteria were associated with the highest prevalence estimates for GDM but were also the criteria published most recently. It was not possible to enter diagnostic criteria in to the multivariate analysis which makes it difficult to assess how much of the increase in prevalence over time was related to the widening of diagnostic criteria and how much it reflected true increases in prevalence. Increases in screening over time also makes interpreting trend in prevalence difficult (Ferrara et al. 2004), although by including only studies using universal screening this source of heterogeneity was removed from this review.

In summary, this is the first meta-analysis to bring together all the relevant evidence relating to GDM prevalence in Europe and to make sense of disparate findings. In the general population of developed Europe, around 1 in 20 pregnant women meet the criteria for GDM. These figures provide a basis for the planning of interventions and health care provision for the prevention of type 2 diabetes. 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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4.6 Critical reflection

Critique of methods

The methods of this systematic review and meta-analysis are the same as the systematic review and meta-analysis reported in chapter three so in depth discussion of the strengths and weaknesses will not be repeated here. In summary, strengths that this review shares with the one reported in chapter three include the fact that independent reviewers were used to screen all of the titles and abstracts identified by the search, decisions about inclusion were discussed and agreed upon by three authors, a thorough quality assessment was conducted for all studies and the majority of studies included were of high quality. As with the review in chapter three, the limited time and resources available for conducting this review meant that only papers published in the English language were included, experts in the field were not contacted, grey literature was not identified, independent double screening was split between two authors, and data extraction was only carried out by one author.

Critique of analysis

As above the general strengths and weaknesses of the analysis used in this paper are covered in chapter three and will not be repeated here. The search for this paper identified no studies published in languages other than English and therefore the critique regarding exclusion of non-English language papers in chapter three is not relevant here. However, there are some issues around the aggregation of studies with diverse methods and outcomes that are specific to GDM. As discussed in relation to IGR in chapter three, there are variations in the way that GDM is screened and the specific criteria used to diagnose GDM. Decisions around which studies should and should not be combined were discussed by the authors at the start of the review process and as a result of these discussions the authors restricted the meta-analysis to studies that used universal screening as opposed to risk based screening to ensure that studies were comparable and the findings were generalizable to the general population of pregnant women. Despite efforts to ensure studies were as comparable as possible, there was heterogeneity in approaches to sampling, methods used to collect blood samples and the criteria used to define GDM. It is argued that summary statistics produced by meta-analyses are meaningless if they aggregate diverse studies (Higgins and Green 2011). However, by using the appropriate model for the meta-analysis, the effect of diversity in study methods

on summary statistics can be reduced. As discussed in the methods section of the paper, the random effects model used in the present study assumes that there is heterogeneity in study methods. A random effects model weights individual studies according to heterogeneity and produces more conservative summary statistics than the alternative fixed effects model, which does not make such assumptions about study heterogeneity (Haidich 2010). A further weakness of paper two was that the search was conducted on one fewer platform than the systematic review in paper one as I no longer had access to EMBASE.

Chapter five: Incidence of impaired glucose regulation and progression to type 2 diabetes (publication three)

Eades, C.E., Leese, G.P. and Evans, J.M.M. (2014) Incidence of impaired glucose regulation and progression to type 2 diabetes mellitus in the Tayside region of Scotland. *Diabetes Research and Clinical Practice*, 104 (1), pp. e16-e19.

This paper was published in Diabetes Research and Clinical Practice, a peer reviewed journal with an impact factor of 3.04, and has been cited four times. It is an international journal that publishes research on diabetes and related areas aimed at health care providers and clinically orientated researchers.

The content of the above publication is presented in this chapter followed by a section providing a critical reflection of the methods. A PDF of the published manuscript can be found in appendix 6. Ethical approval for this study was obtained from the School of Nursing, Midwifery and Health Research Ethics Committee at the University of Stirling (see appendix 7 for a copy of the approval letter). The NHS Tayside Committee for Medical Research Ethics have granted approval for studies using routinely collected anonymised health data provided that the Standard Operating Procedures (SOPs) for the anonymisation and release of data are followed. The SOPs for the Health Informatics Centre (HIC), who provided the data, were closely followed during this study. A copy of the NHS Research and Development approval obtained for this study can be found in appendix 8.

A verbatim copy of publication three starts below.

5.1 Abstract

This study assessed incidence of impaired glucose regulation (IGR) and progression to type 2 diabetes in adults in one region of Scotland using routinely collected health-care data. Incidence of IGR was 2,720 per 100,000 person years. Nine per cent of IGR patients progressed to type 2 diabetes in a mean time of 34 months.

5.2 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 criteria for type 2 diabetes. These two states of Impaired Glucose Regulation (IGR) confer an increased risk of developing type 2 diabetes (Unwin et al., 2002). Research has shown that progression from IGR to type 2 diabetes can be prevented through lifestyle changes meaning that a diagnosis of IGR could offer an ideal opportunity to deliver preventative interventions (Davies et al. 2004). In order to assess the feasibility of an intervention with IGR patients it is important to assess the rate of identification of IGR by health care providers and to characterise progression to type 2 diabetes. Recent research in the United States has reported prevalence rates of IGR in the general population as high as 35% (Kavre and Hayward 2010). There has been little research on this topic conducted in the United Kingdom. The present study assessed incidence of IGR and characterises progression from IGR to type 2 diabetes in adults in one region in Scotland using routinely collected health-care data.

5.3 Methods

Study design

The study adopted an observational retrospective cohort design using anonymised patient data for the complete population of Tayside, Scotland, UK (approx. population 400,000). Data were provided by the Health Informatics Centre (HIC) at the University of Dundee, and the main data set used was SCI-DC which is a validated diabetes clinical information system (Morris et al. 1997).

Population

HIC provided patient demographic information (i.e. gender, date of birth, and deprivation from the Scottish Index of Multiple Deprivation [SIMD]; Scottish Executive 2010) and all instances of blood glucose testing in the population of Tayside from January 2003 to December 2008. This totalled 2,119,177 tests after excluding non-valid records (e.g. damaged samples). Patients were classified as having IGT or IFG if they had undergone two blood glucose tests on the same date (one coded in the records as a fasting test with the second test assumed to be carried out after an oral glucose tolerance test) that met the WHO (2006) criteria for IGT and IFG (IGT - first test < 7.0 mmol/l and second test 7.8-

11.0 mmol/l; IFG - first test 6.1-6.9 mmol/l; second test <7.8 mmol/l). However, the majority of patients were found to have only taken a fasting test. Although the WHO criteria allow a single fasting test to be used to diagnose IFG, it also states that this classification is uncertain. In order to avoid loss of relevant data, patients with only one fasting glucose test of 6.0-6.9 mmol/L were classified as having undefined IGR (uIGR). Patients meeting any of the above criteria for IGR were included in the study if aged 18 and over with no previous diagnosis of type 2 diabetes. Figure 3 illustrates selection of patients in the study. Patients with IGR were followed up for diagnosis of type 2 diabetes using the SCI-DC database which held complete data up to December 2011. Patients with type 2 diabetes are defined as those who are diagnosed with diabetes over the age of 35 years, or younger patients for whom there is no immediate requirement for insulin. The precise glucose levels used to diagnose type 2 diabetes depend upon the criteria used at the time of diagnosis.

Analysis

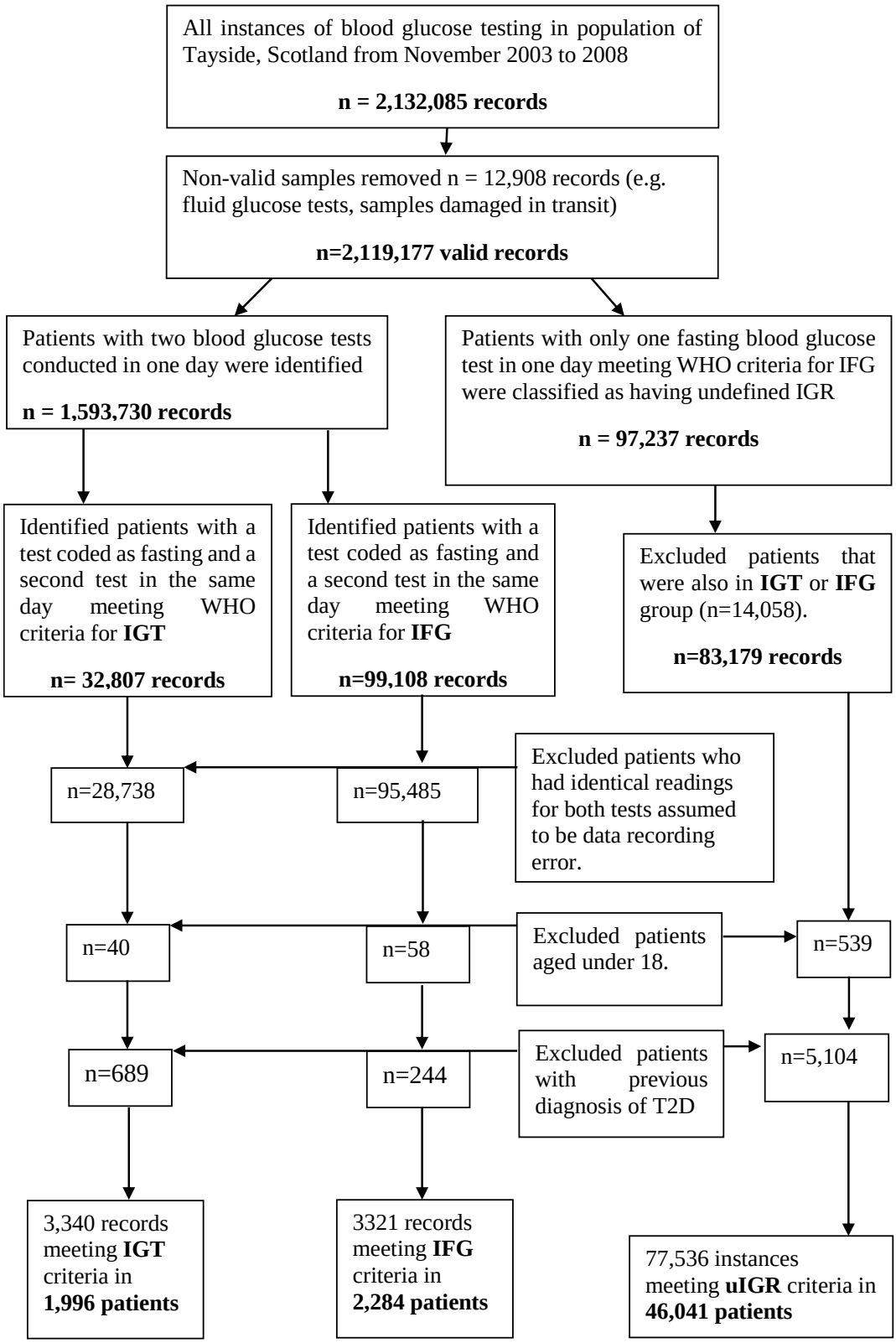
Incidence rates of IGT, IFG and uIGR were calculated by dividing the number of new cases in one year by the population of Tayside aged over 18 in the same year. The relationship between potential risk factors and development of type 2 diabetes was assessed by univariate and multivariate Cox regression, from which hazard ratios (HRs) and 95% CIs were calculated. Age, gender, deprivation category and type of IGR were entered as independent variables, with diagnosis of type 2 diabetes as the dependent variable. Statistical analyses were carried out using SPSS for Windows version 19. Ethical approval was obtained from the School of Nursing, Midwifery and Health at the University of Stirling. The Tayside Committee for Medical Research Ethics have granted approval for studies using routinely collected, anonymised health data.

5.4 Results

Incidence of impaired glucose regulation

In total 50,321 patients were identified who met the criteria for either IFG (n=2284), IGT (n=1996) or uIGR (n=46041) during the study period (2003 to 2008). Of the 50,321 patients identified, 52.3% were female and the mean age at diagnosis was 62.8 (S.D.=17.2). The total incidence across the study period was 2,720 per 100,000 person years.

Figure 3: The identification of participants with impaired glucose regulation from the biochemistry data supplied by the Health Informatics Centre.



No significant differences were found in incidence of all types of IGR by gender ($t(10)=0.253$, $p=0.897$) or deprivation category ($F(4)=0.21$, $p=0.930$). Incidence differed significantly by age category ($F(3)=39.44$, $p<0.001$) with a steady increase in incidence noted with increasing age.

Progression to type 2 diabetes

A total of 4,548 patients with IGR (9%) were diagnosed with type 2 diabetes during the study with a mean time of 34 months between IGR and type 2 diabetes diagnosis. Table 11 shows that men with IGR were at a small but significantly increased risk of developing type 2 diabetes compared to women, as were more deprived patients compared to the least deprived. The risk of progression to type 2 diabetes increased with increasing age. Patients with IGT were found to be at a small but significantly increased risk of developing type 2 diabetes compared to those with IFG or uIGR. These associations were evident in univariate and multivariate analyses. Mean time for progression from IGR to type 2 diabetes was largely similar in high risk groups of patients, as for all patients who developed type 2 diabetes in the study.

5.5 Discussion

To the best of our knowledge this study is the first to investigate the incidence of IGR and progression to type 2 diabetes in the UK. We found that a considerable number of people were diagnosed with IGR over the study period, of whom nearly 10% of developed type 2 diabetes within a relatively short time frame. However, a mean time of nearly three years between diagnosis of IGR and type 2 diabetes does provide sufficient opportunity for an intervention to be delivered and lifestyle changes to be made. Those people with IGR at the highest risk of developing type 2 diabetes are those with IGT and from a deprived background: as such, these patients should arguably be prioritised within prevention programmes. The use of routinely collected patient data means that the rates of IGR reported here may not be reflective of the true rates in the general population. However, this methodology gives the findings greater clinical relevance which is of the highest importance if interventions are to be developed for use in this setting.

Table 11: Hazard ratio of developing type 2 diabetes in patients with all type of IGR according to sex, age, deprivation category and type of IGR

	Univariate				**Multivariate**	
Sex	**No. (%) progressing to type 2 diabetes**	**Mean time to progress (months)**	**Hazard ratio (95% CI)**	**p value**	**Hazard ratio (95% CI)**	**p value**
Women	2114 (8.2)	33.9	1.00		1.00	
Men	2408 (10.2)	34.4	1.26 (1.19-1.34)	<0.001	1.1 (1.04-1.17)	0.002
Age at diagnosis of IGR						
18-27	14 (1.2)	30.9	1.00		1.00	
28-37	62 (2.5)	14.2	2.16 (1.21-3.87)	0.009	2.14 (1.2-3.83)	0.010
38-47	330 (8.0)	38.6	6.89 (4.03-11.75)	<0.001	6.73 (3.94-11.49)	<0.001
48-57	794 (12.0)	35.5	10.6 (6.24-17.97)	<0.001	10.21 (6.02-17.32)	<0.001
58-67	1320 (13.5)	35.2	12.01 (7.1-20.33)	<0.001	11.62 (6.86-19.67)	<0.001
68-77	1289 (11.9)	33.4	10.26 (6.06-17.37)	<0.001	9.96 (5.89-16.87)	<0.001
78-87	629 (6.2)	30.6	5.25 (3.09-8.92)	<0.001	5.14 (3.02-8.72)	<0.001
88 plus	84 (2.0)	22.3	1.68 (0.95-2.95)	0.072	1.68 (0.96-2.95)	0.072
Deprivation Category						
5 least deprived	752 (8.3)	35.1	1.00		1.00	
4	1315 (8.5)	34.8	1.2 (1.09-1.33)	<0.001	1.18 (1.07-1.31)	0.001
3	820 (9.4)	33.2	1.19 (1.08-1.32)	0.001	1.21 (1.01-1.34)	<0.001
2	775 (9.8)	34.8	1.14 (1.14-1.04)	0.008	1.15 (1.04-1.27)	0.006
1most deprived	794 (9.9)	32.3	1.03 (0.94-1.12)	0.569	1.04 (0.95-1.13)	0.431
Type of IGR						
IGT	247 (12.6)	28.5	1.00		1.00	
IFG	182 (8.1)	33.4	0.64 (0.53-0.78)	<0.001	0.64 (0.53-0.78)	<0.001
uIGR	4093 (9.1)	34.5	0.73 (0.64-0.83)	<0.001	0.73 (0.64-0.83)	<0.001

This is the end of the verbatim copy of the publication three.

5.6 Critical reflection

Critique of methods

This study has a number of strengths. The use of routinely collected health care data gives the findings greater clinical relevance which is of the highest importance if they are to be used to inform care delivery or the development of an intervention for this setting. Use of routinely collected health care data also allowed access to a large amount of data which could not have been collected using primary data collection methods with the resources available. The data for this study came from the Tayside Health Board in Scotland which has a population of around 400,000 people. Tayside Health Board is demographically similar to the wider population of Scotland with the same sex-ratio and similar median age and population density (National Record of Scotland 2017) and very similar incidence and prevalence of diabetes (Scottish Diabetes Survey 2017). The findings of the present study are therefore likely to be generalisable to the wider population of Scotland.

The diagnoses of type 2 diabetes were made using a validated diabetes clinical information system SCI-DC that has been extensively used in health care research. SCI-DC utilises a unique patient identifier that is assigned to every patient in Scotland upon registration at a general practitioner called the community health index (CHI) number to link electronic records on diabetes. The CHI consists of 10 digits, with the first six digits containing the patient's date of birth. A centrally held, continuously updated record contains data on the patient's address, postcode, general practitioner, death and date of death and this is linked to their CHI. The CHI is recorded and used as the patient identifier for the majority of primary and secondary healthcare activities in Scotland. SCI-DC links data from a number of independent sources to identify cases of diabetes. Deterministic linkage is used in SCI-DC where possible to identify cases of diabetes, with CHI the unique patient identifier. In cases where CHI has not been recorded, for example in prescription and ambulance service data, probabilistic linkage is used instead.

The original SCI-DC database for Tayside (known as DARTS) was set up to allow all patients with diabetes to be identified in order to improve diabetes care (Morris et al. 1997). At the time that DARTS was set up, registers only usually included people treated

with insulin making it difficult to identify people with type 2 diabetes. The registers that did exist were typically created by aggregating records held be general practices or by combining these general practice registers with those of hospital diabetes clinics. The DARTS study aimed to test the central linkage of electronic records relating to diabetes from multiple independent sources and hypothesised that linkage of electronic records would be more efficient and effective method of identifying people with diabetes than general practice lists. The study found that electronic record linkage was more sensitive at identifying people with diabetes with a sensitivity of 95% for electronic record linkage compared to 91% for GP lists (Morris et al. 1997).

Although the electronic record linkage used in this study has been shown to have good sensitivity for identifying diabetes, there are limitations to this method. When data-sets are linked, a proportion of cases will match and a proportion will remain unmatched. In false negative errors in data linkage, records that correspond to the same person cannot be linked and in false positive errors records that do not correspond to the same person are incorrectly linked (Bohensky et al. 2010). Broader issues with data collected in routine health care practice can compound these issues. Standards of data collected in routine health practice are often not as high as those expected for research purposes and there can be inconsistent coding of data and missing or inaccurate data. Much health care data is still recorded manually and the transfer of these data to electronic forms introduces further risk of human errors (Kane et al. 2000). Indeed, the number of years of data available for analysis in this study was limited, partly because of issues with recording of data. Biochemistry data for this study were available from 1998 and complete up until 2008. However, analysis of the data showed that only 3% of people in the study who met the criteria for IGR were diagnosed between 1998 and 2002 and the data included in the study was therefore limited to between 2003 and 2008. It is likely that the small number of patients identified in the earlier study years is a reflection of lower rates of testing but also poorer recording of IGR data. It is important that these limitations are recognised and that the results of this study are interpreted accordingly.

A further weakness of this study is that it was not possible to determine the exact nature of the second test used to diagnose patients as having IFG or IGT. It is possible that the presence of a second blood glucose test in one day could represent something other than an oral glucose tolerance test (e.g. pre and post-operative blood glucose testing), thus

there may be patients in the sample who are falsely classified as having IGT or IFG. However, patients classified using two tests in one day make up only a minority of the sample so it is unlikely that the proportion of patients falsely identified as having IGT or IFG is high. People were also classified on the basis of a fasting test alone and some of these patients might have been diagnosed with type 2 diabetes if a glucose tolerance test had been performed. However, this is unlikely to be a major confounder as those with uIGR actually had a lower rate of developing type 2 diabetes than those with IGT.

Both the ADA (2011) and WHO (2011a) now recommend that HbA1c can be used in the diagnosis of IGR and research has shown that HbA1c and FPG/2hPG tests do not identify the same people as being at high risk of type 2 diabetes (Mann et al. 2010; Barry et al. 2017). By only using FPG/2hPG to identify people with IGR and not HbA1c, publication three is likely to have missed a portion of the population who are at high risk of type 2 diabetes.

A further limitation associated with the use of routinely collected data in this study is that the rates of IGR reported may not be reflective of the true rates in the general population, as there may be some people with IGR who have not been detected by the health service. This study used the adult population of Tayside as the denominator in the calculation of incidence of IGR. The presence of people with undiagnosed IGR in the general population of Tayside means it is likely that this study has underestimated the incidence of IGR. An alternative to using the entire adult population of Tayside as the denominator would have been to use all people with instances of blood testing in Tayside. This option was considered during the analysis but because people who have a blood test are arguably more likely to be higher risk patients, it may have resulted in an overestimation of incidence and the decision was made to take the more cautious approach to calculating incidence. A weakness of the analysis in publication three was that a key assumption of the Cox's hazard model was not assessed. The proportional hazards assumption requires that the ratio of hazards for individuals in the study remains constant over time. It was assumed in this study that the proportional hazards assumption was not violated but this could have been tested by creating a time dependent covariate and including this in the model. If this covariate was statistically significant then the proportional hazards assumption has been violated.

Ethical considerations

As this study used anonymised secondary data, there were only very limited risks to those involved in the study. The main risk to patients was breach of confidentiality. However, this risk was very small as all data in this study were anonymised and did not contain any identifiable information about patients. Anonymisation was carried out by the provider of the data, HIC, prior to the data being passed on to the researcher. The unique patient identifier assigned to every patient in Scotland called the community health index (CHI) was anonymised by HIC into a project specific pseudo-CHI. Date of birth data were anonymised by changing the day of birth to the 1st and the month to the middle of the appropriate quarter year. For example, a patient born on the 24th of January 1975 would be anonymised to the 1st of February 1975. Postcode was restricted to district by removing the last three digits (Galloway 2010). The anonymised data were stored on a secure server provided by HIC and accessed remotely. This server meant that data did not need to be stored on the researcher's own computer but instead were accessed and analysed on a restricted, secure IT environment. The researcher was unable to print, access the internet or export data while on the secure server thus reducing the risk of the data being accessed by anyone else. Data outputs (e.g. tables or statistical analyses) were reviewed by HIC prior to being released to the researcher and HIC Standard Operating Procedures were adhered to at all times when working with the data (HIC 2016).

Informed consent was not sought from participants in this study as the National Research Ethics Service guidance states that it is not an ethical or legal requirement for research using anonymised health care data (HIC 2016). Informed consent is when someone agrees to take part in research on the basis of having full access to information about what participation involves, including the potential harms and benefits (Royal College of Nursing 2011). Informed consent is a central part of research ethics and is embedded in various ethical codes such as The Declaration of Helsinki (World Medical Association 2001). The process of gaining informed consent ensures that people who participate in research understand fully what this will involve, and that they are not coerced into participating.

Although informed consent was not required in the present study, not seeking consent clearly raises ethical issues. It is possible that the people whose data were used in the

present study would be unaware and/or unhappy about the use of their data in this way. Hill et al. (2013) carried out a systematic review and qualitative study to explore public attitudes towards the secondary use of existing health care data. The systematic review reported that in the majority of studies, participants were not aware of how their medical data might be used for research and expressed a wish to be informed about how and by whom their data were being used. Although not aware of these potential uses, participants in the majority of studies recognised the benefit that medical research could have for the general population and often discussed the balance between obtaining consent and the benefits of unrestricted research. Despite recognising these benefits, many participants felt that informed consent should always be sought for research using medical data. Similar findings were reported in the focus groups carried out by Hill et al. (2013). However, focus group participants became more accepting of the use of medical data without consent after being given information about research processes and biases. Focus group participants were also more accepting of research using their medical data undertaken by the NHS compared to research for financial gain, for example, by pharmaceutical companies.

Given that the participants in the Hill et al. (2013) study agreed to participate in this study, it is likely that their views on the topic were more positive than those of the general population. The research by Hill et al. (2013) suggests that some participants in the present study may not have been aware or accepting of the use of their data for this research. However, data in the present study were up to ten years old which would have made seeking consent very challenging. In addition to the practical challenges, it is suggested that seeking informed consent can affect the validity of research by introducing selection bias. Selection bias is where there are systematic differences between people who agree to participate in research and those who do not. A systematic review by Kho et al. (2009) reported that there were significant differences between participants and non-participants in prospective observational studies using medical data where informed consent was sought. It can be argued that NHS medical data is a publicly funded resource that should be utilised where possible for public benefit and that the benefits of having access to medical data without the need to seek informed consent outweigh the ethical issues.

Chapter six: Progression from gestational diabetes to type 2 diabetes (publication four)

Eades, C., Styles, M., Leese, G.P., Cheyne, H. and Evans, J.M.M. (2015) Progression from gestational diabetes to type 2 diabetes in one region of Scotland: an observational follow up study. *BMC Pregnancy and Childbirth*, 15, 11. Available: https://doi.org/10.1186/s12884-015-0457-8 [Accessed 6 October 2018].

This paper was published in BMC Pregnancy and Childbirth, an open access peer reviewed journal that publishes on all aspects of pregnancy and childbirth with an impact factor of 2.18, and has been cited 9 times.

The content of the above publication is presented in this chapter followed by a section providing a contextualising narrative. Ethical approval for this study was obtained from the School of Nursing, Midwifery and Health Research Ethics Committee at the University of Stirling (see appendix 7 for a copy of the approval letter). The NHS Tayside Committee for Medical Research Ethics have granted approval for studies using routinely collected anonymised health data provided that the Standard Operating Procedures (SOPs) for the anonymisation and release of data are followed. The SOPs for the Health Informatics Centre (HIC), who provided the data, were closely followed during this study. A copy of the NHS Research and Development approval obtained for this study can be found in appendix 8. A PDF of the published manuscript can be found in appendix 9.

A verbatim copy of publication four starts below.

6.1 Abstract

Background

The aim of this study was to investigate long-term risk of type 2 diabetes following a diagnosis of gestational diabetes mellitus (GDM) and to identify factors that were associated with increased risk of type 2 diabetes.

Methods

An observational cohort design was used, following up all women diagnosed with GDM attending a Diabetes Antenatal Clinic in the Dundee and Angus region of Scotland between 1994 and 2004 for a subsequent diagnosis of type 2 diabetes, as recorded on SCI-DC (a comprehensive diabetes clinical information system).

Results

There were 164 women in the study who were followed up until 2012. One quarter developed type 2 diabetes after a pregnancy with GDM in a mean time period of around eight years. Factors associated with a higher risk of developing type 2 diabetes after GDM were increased weight during pregnancy, use of insulin during pregnancy, higher glycated haemoglobin (HbA1c) levels at diagnosis of GDM, and fasting blood glucose.

Conclusions

These findings suggest there is a viable time window to prevent progression from GDM to type 2 diabetes and highlights those women who are at the greatest risk and should therefore be prioritised for preventative intervention.

6.2 Background

Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance that begins or is first detected during pregnancy. GDM can have health consequences for the mother and baby both in the short and longer term. Although normal glucose regulation usually returns shortly after delivery, women diagnosed with GDM have at least a seven fold increased risk of developing type 2 diabetes in the future (Bellamy et al. 2009). In Europe, GDM affects between 2-6% of pregnancies but research has shown that the incidence of GDM has been rising (Buckley et al. 2012; Ferrera 2007).

Type 2 diabetes is a growing public health concern associated with a number of serious health complications that reduce both the life-expectancy and quality of life of sufferers (Donnelly et al. 2000; Colagiuri et al. 2006). There is good evidence to suggest that lifestyle interventions targeted at those at high risk of type 2 diabetes, such as those with pre-diabetes, can prevent or at least delay the onset of type 2 diabetes (Gillies et al., 2007). A diagnosis of GDM therefore represents a window of opportunity for preventative intervention. However, there has been little research on interventions designed specifically for women with GDM, and none in the UK to our knowledge. In order to be able to assess the feasibility and practicality of a lifestyle intervention targeted at women with GDM, it is important to establish the nature of the progression from GDM to type 2 diabetes in the UK context. A systematic review of studies assessing the association between GDM and type 2 diabetes did not report any research that had been conducted in the United Kingdom (Kim et al 2002). This study therefore characterises the progression of GDM to type 2 diabetes in the Dundee and Angus region of Scotland, UK.

6.3 Methods

Study design and population

This observational study used historical routinely collected health-care data to follow up women diagnosed with GDM. Antenatal care is a universal service accessed by almost all pregnant women in Scotland. Women diagnosed with GDM during routine antenatal care in the Dundee and Angus region (approximate population 250,000) attend the Diabetes Antenatal Clinic at Ninewells Hospital in the city of Dundee. All women in Dundee and Angus were screened with a fasting blood glucose (FBG) or random blood glucose (RBG) at 28 weeks gestation. All patients with any abnormal result (RBG of >5.5mmol/l^{-1} two or more hours after food or >7.0mmo/l^{-1} within two hours of food; FBG >5.5mmol/l^{-1}), any glycosuria and all high risk pregnancies underwent a 75g oral glucose tolerance test (OGTT). All women diagnosed with GDM who had attended this clinic between 1994 and 2004, and who had no previous diagnosis of type 1 diabetes or type 2 diabetes were included in this study. Women diagnosed with GDM in the first trimester of pregnancy were excluded as these women were likely to have had undiagnosed pregestational diabetes (International Association of Diabetes and Pregnancy Study Group [IADPSG], 2010). GDM was diagnosed on the basis of clinical guidance in use at

the time of the study which suggested an FBG of greater than 5.5mmol/l^{-1}or a blood glucose reading two hours (2h BG) after an OGTT of greater than 9mmol/l^{-1}.

Data were extracted from paper based case records held at Ninewells Hospital containing clinical and personal data for all women who had attended the diabetes antenatal clinic between 1994 and 2004. These records included the following forms: a booking form which was completed at the first visit to the clinic after a diagnosis of GDM; follow up forms for each further visit to the clinic and a postnatal form containing information from a postnatal check-up. The information extracted from these forms included the mother's date of birth, family history of diabetes, history of GDM in a previous pregnancy, parity, birth weight of previous babies, week of gestation, OGTT fasting and 2 hour blood glucose levels at booking and postnatal (where recorded), mother's weight, Hba1C and treatment during pregnancy. Week of gestation, mother's weight and HbA1c were extracted from the booking, follow up and postnatal forms where recorded.

Data extracted from the paper based records were anonymised and linked to SCI-DC, a validated diabetes clinical information system (Morris et al., 1997), by the Health Informatics Centre at the University of Dundee (HIC). Patients were followed up for a diagnosis of type 2 diabetes using the Scottish Care Information – Diabetes Collaboration (SCI-DC) system which holds complete information on patients diagnosed with type 2 diabetes in Scotland up to March 2012. Women who died or migrated out of the health board during the follow up were not excluded from the study but the date of death/migration was used as their study end date in the analysis.

Patients with type 2 diabetes are defined as those who are diagnosed with diabetes over the age of 35 years, or younger patients for whom there is no immediate requirement for insulin. World Health Organisation (WHO) criteria were used to diagnose type 2 diabetes but the precise glucose levels used depended upon the criteria in use at the time of diagnosis. The majority of women included in the study (97%) were diagnosed using the WHO criteria published in 1999 (WHO 1999) which defines type 2 diabetes on the basis of a fasting plasma venous sample of 7.0 mmol/l^{-1} or higher and a 2 hour post OGTT value of 11.1 mmol/l^{-1}. The remainder were diagnosed using the WHO 1985 criteria (WHO 1985) which had a higher value for fasting venous plasma of 7.8 mmol/l^{-1} or higher but the same 2 hour value. The data were also linked to a portion of the ISD SMR02 dataset which provided demographic information not available from paper based

records such as deprivation category from the Scottish Index of Multiple Deprivation (SIMD; Scottish Executive 2010) and body mass index (BMI). The SIMD deprivation category is a postcode measure derived from multiple aspects of deprivation including employment, income, health, education, access to services, crime and housing.

Analysis

In survival analyses, women were followed up from the date of diagnosis of gestational diabetes. Women who had more than one pregnancy during the study period were followed up from the earliest date of diagnosis of gestational diabetes. The relationships between potential risk factors and development of type 2 diabetes were assessed by univariate and multivariate Cox regression, from which hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Deprivation category, age, history of GDM, family history of diabetes, use of insulin during pregnancy, average weekly weight gain and weight, trimester, glycated haemoglobin (HbA1c), FBG, 2h BG at diagnosis of GDM were entered as independent variables, with diagnosis of type 2 diabetes as the dependent variable. Statistical analyses were carried out using SPSS for Windows version 21. Ethical approval was obtained from the School of Nursing, Midwifery and Health at the University of Stirling. The Tayside Committee for Medical Research Ethics has granted approval for studies using routinely collected, anonymised health data and this study falls under this approval.

6.4 Results

Characteristics of population

Data were extracted from the records for 285 women, of which 164 women met the criteria for GDM and had no previous diagnosis of type 1 diabetes or type 2 diabetes, and were therefore included in the study. Of the remainder 75 women had type 1 diabetes, 12 had type 2 diabetes, 2 were diagnosed with GDM in the first trimester and 1 had maturity onset diabetes of the young. A further 21 women were classified as borderline GDM as their blood glucose results were high but did not meet the criteria for GDM. Ten women with GDM were excluded due to having missing data or a previous diagnosis of type 1 diabetes or type 2 diabetes.

At the time of diagnosis of GDM, women ranged in age from 16 to 43 with a mean age of 30. Table 12 shows further characteristics of the population. Women were more

commonly from areas of higher deprivation than lower deprivation. A positive family history of diabetes was noted for around a third of women and the majority were having their first or second child. BMI data were not recorded for the majority of women in this study.

Table 12: Characteristics of the population

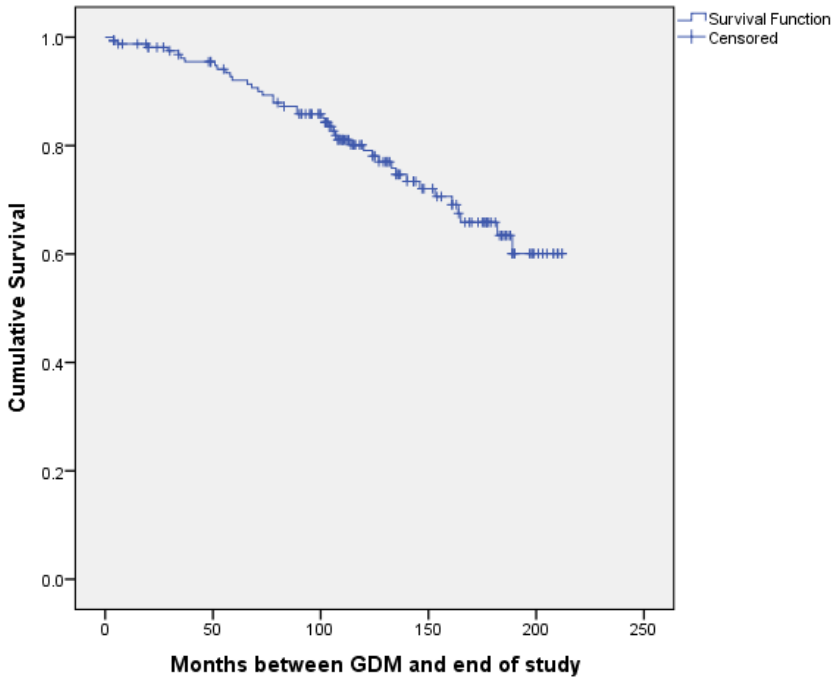
Deprivation Category	**n (%)**
5 (Lowest Deprivation)	17 (10.4)
4	39 (23.8)
3	21 (12.8)
2	35 (21.3)
1 (Highest Deprivation)	44 (26.8)
Data Missing	8 (4.9)
Previous Live Births	**n (%)**
0	57 (34.8)
1	54 (32.9)
2	28 (17)
3 or more	19 (11.6)
Data Missing	6 (3.7)
Mother's weight (kg)	**n (%)**
Up to 76.8	46 (28)
76.8-92.5	49 (29.9)
Over 92.5	53 (32.3)
Data Missing	16 (9.8)

Progression to type 2 diabetes

Forty one women (25%) developed type 2 diabetes during follow-up. The time between diagnosis of GDM and type 2 diabetes ranged from 4 months to nearly 16 years, with a mean time of 93 months (SD=48.2) or nearly 8 years. Of these women only 3 (7.3%) went on to develop type 2 diabetes in the two years after their diagnosis of GDM and a further 4 (9.8%) developed type 2 diabetes two to four years after their diagnosis of GDM. Figure 4 shows a relatively steady rate of type 2 diabetes incidence after diagnosis of GDM over the study period. Table 13 shows the results of both univariate and multivariate Cox survival analysis. Greater weight during pregnancy, insulin use during pregnancy, higher HbA1c levels and FBG were associated with highly elevated risks of progression to type 2 diabetes in univariate and multivariate analyses. Although 2hBG and were also associated with an increased risk univariately, this association was no

longer statistically significant after adjusting for other variables. While there were no statistically significant associations for increasing age, family history of type 2 diabetes or previous history of GDM, the hazard ratios were elevated. There was no evidence for an association with deprivation or average weekly weight gain.

Figure 4: Cumulative incidence of type 2 diabetes after diagnosis of GDM



6.5 Discussion

To the best of our knowledge this study is the first to investigate progression from GDM to type 2 diabetes in the UK. We found that around a quarter of women diagnosed with GDM developed type 2 diabetes with a mean time window between the two diagnoses of 8 years. The vast majority of women who did develop type 2 diabetes after GDM did so five years or more after their diagnosis of GDM. This time period presents a considerable window of opportunity to deliver an intervention and for women to make necessary changes to their diet and activity levels in order to reduce the risk of progression to type 2 diabetes. Many people find making lifestyle changes difficult and women who have recently had a baby face additional problems. For example, a lack of time is often cited by women who have had GDM as a barrier to making lifestyle changes (Parsons et al. 2014).

Table 13: Hazard ratio of developing type 2 diabetes in patients with GDM according to previous history of GDM, family history of diabetes, deprivation category; insulin use and average weekly weight gain during pregnancy; and weight, age, trimester, HbA1c, fasting and 2 hour blood glucose at diagnosis of GDM

		Univariate			Multivariate	
	No. (%) progressing to type 2 diabetes	**Mean time to progress (months)**	**Hazard ratio (95% CI)**	**p value**	**Hazard ratio (95% CI)**	**p value**
Whole sample (n=164)	41 (25)	93				
Deprivation Category (no. in each group)						
5 least deprived (17)	2 (12)	21	1.00		1.00	
4 (39)	8 (21)	78	1.44 (0.31-6.76)	0.647	0.68 (0.12-3.95)	0.671
3 (21)	6 (29)	94	1.86 (0.38-9.20)	0.448	0.71 (0.11-4.61)	0.717
2 (35)	13 (37)	115	2.81 (0.63-12.45)	0.174	1.92 (0.37-10)	0.438
1 most deprived (44)	11 (25)	82	1.76 (0.39-8.89)	0.461	0.76 (0.15-3.93)	0.742
Data missing (8)	1 (13)	106	0.81 (0.07-8.89)	0.860	0.9 (0.07-11.96)	0.936
Age (no.)						
25 and under (32)	6 (19)	99	1.00		1.00	
26 to 34 (84)	19 (23)	93	1.28 (0.51-3.19)	0.604	1.35(0.48-3.79)	0.570
35 and over (48)	16 (33)	86	1.90 (0.74-4.87)	0.179	2.38 (0.82-6.95)	0.112
Previous history of GDM (no.)						
Yes (11)	4 (36)	83	1.7 (0.61-4.77)	0.315	2.83 (0.62-12.87)	0.179
No/Data missing (153)	37 (24)	91	1.00		1.00	
Family history of Diabetes (no.)						
Yes (59)	17 (29)	89	0.80 (0.43-1.49)	0.485	1.42 (0.64-3.15)	0.385
No/Data missing (105)	24 (23)	93	1.00		1.00	

		Univariate			Multivariate	
	No. (%) progressing to type 2 diabetes	**Mean time to progress (months)**	**Hazard ratio (95% CI)**	**p value**	**Hazard ratio (95% CI)**	**p value**
Weight (kg)						
76.8 to 92.5kg (49)	15 (31)	88	5.19 (1.5-17.93)	0.009	4.98 (1.23-20.18)	0.024
Over 92.5kg (53)	20 (38)	89	6.49 (1.93-21.86)	0.003	5.22 (1.38-19.73)	0.015
Data missing (16)	3 (19)	150	3.05 (0.62-15.12)	0.172	3.5 (0.53-23.34)	0.196
Trimester at diagnosis (no.)						
2nd trimester (16)	5 (31)	96	1.21 (0.47-3.07)	0.696	1.05 (0.32-3.45)	0.942
3rd trimester (147)	36 (24)	90	1.00		1.00	
HbA1c in mmol/mol (no.)						
33.3 and under (19)	3 (16)	150	1.00		1.00	
33.3 to 42.1 (22)	5 (23)	82	1.42 (0.34-5.95)	0.630	1.59 (0.29-8.84)	0.597
42.1 plus (18)	8 (44)	57	4.41 (1.17-16.69)	0.029	5.34 (0.98-29)	0.052
Data missing (105)	25 (24)	98	1.66 (0.5-5.5)	0.407	1.9 (0.45-7.94)	0.381
Fasting Blood Glucose in mmol/l (no.)						
Under 5.1 (52)	6 (12)	102	1.00		1.00	
5.1 to 7.0 (72)	20 (28)	93	2.62 (1.05-6.53)	0.038	1.66 (0.52-5.24)	0.392
Over 7.0 (17)	6 (35)	60	6.87 (2.2-21.44)	0.001	3.94 (0.92-16.91)	0.065
Data missing (23)	9 (39)	99	3.87 (1.38-10.89)	0.010	35.29 (2.18-570.68)	0.012
2 hour post load blood glucose in mmol/l (no.)						
Under 8.5 (39)	7 (18)	83	1.00		1.00	
8.5-11.1 (67)	14 (21)	96	1.15 (0.46-2.85)	0.762	1.54 (0.54-4.38)	0.417
Over 11.1 (36)	12 (33)	84	2.58 (1.01-6.56)	0.047	2.37 (0.76-7.4)	0.139
Data missing (22)	8 (36)	99	2.13 (0.77-5.88)	0.144	0.1 (0.01-1.56)	0.101
Used Insulin during pregnancy (no.)						
Yes (51)	20 (39)	88	2.82 (1.52-5.2)	0.001	2.81 (1.35-5.86)	0.006
No (113)	21 (19)	94	1.00		1.00	
Average weekly weight gain (kg)						
0.3 and under (61)	16 (26)	82	1.00			
0.31 and above (64)	14 (22)	90	0.71 (0.35-1.47)	0.360	0.61 (0.2-1.45)	0.259
Data Missing (39)	11 (28)	105	1.04 (0.49-2.25)	0.912	1.12 (0.43-2.93)	0.821

Our findings suggest that the window of opportunity may be large enough for the majority of women to allow an intervention to be delayed until the child is slightly older and less dependent. Such a delay may help to address some of the barriers to lifestyle change faced by women with GDM but this argument becomes complex if women are planning to have more children. This issue is further complicated by the fact some women have already made lifestyle changes during pregnancy in an attempt to manage their GDM. With these women it may be best to intervene sooner after pregnancy to ensure these changes are maintained. The timing of lifestyle interventions for women who have had GDM clearly needs further exploration with women, along with the optimal content and means of delivery, if interventions are to be successful.

Women who were at highest risk of developing type 2 diabetes after GDM were heavier women, those with an HbA1c of over 42.1mg/dL, those who used insulin during their pregnancy and those with FBG of 7.0 mmol/l and over. These women should arguably be prioritised for intervention. These findings are largely consistent with previous research reported in a systematic review of studies assessing the incidence of type 2 diabetes after a diagnosis of GDM (Kim et al. 2002).

Higher FBG levels and HbA1c were associated with higher risk univariately, but this increased risk was only marginally significant in the multivariate analysis. However, we identified an increased risk of four fold for women who had an FBG of 7.0 and over five fold for women with an HbA1c of over 42.1mg/dL. Given the small sample size and wide confidence intervals in this study, these marginally significant risks cannot be discounted. It is difficult to compare our finding for FBG with previous research that has generally looked at FBG as a continuous variable; thus particular thresholds of FBG for increased risk of type 2 diabetes have been difficult to pinpoint. Studies that did use categories for FBG reported varying findings. One study found an 11 fold risk in women who had an FBG of 5.9 or over compared to those with lower FBG values (Steinhart et al. 1997). Two other studies reported that women who went on to develop type 2 diabetes had a mean FBG of closer to 8.0 (Catalano et al. 1991; Kjos et al. 1990).

The systematic review of studies assessing the incidence of type 2 diabetes after a diagnosis of GDM (Kim et al. 2002) reported mixed findings for the association between BMI and future type 2 diabetes risk. There were insufficient data for BMI in the present study to include it in the survival analysis. However, weight was found to be significantly

associated with increased risk of type 2 diabetes in the multivariate analysis, with other factors such as trimester controlled for. Although weight is typically regarded as an unreliable measure of obesity and disease risk as it does not take into account height, our study does suggest that it may be a useful indicator of future risk of type 2 diabetes in women with GDM.

We did not find statistically significant associations between increasing age, history of GDM in a previous pregnancy or family history of diabetes and future risk of type 2 diabetes. Although the hazard ratio estimates were elevated, particularly for previous history of GDM, and therefore increased risks cannot be discounted, the sample size in our study was relatively small and confidence intervals were wide. Previous research reports mixed results for these risk factors; therefore larger studies are required to verify the results.

Despite being a small study, the diagnosis of GDM in our sample of 164 women was validated for each one and we are confident in the high quality of our data. Detailed information was collected from paper records using a pre-defined data collection tool. The subsequent type 2 diabetes diagnoses were made using a diabetes clinical information system that has been extensively used in health care research and is known to be accurate. However, with around 2,600 births per year in Dundee and Angus, it is clear that we did not identify all cases of GDM during the study period. We would have expected to identify between 500 and 600 women over the period of the study using a conservative rate of 2% of pregnancies affected by GDM. On the other hand, we know that the women that we did include definitely had GDM, even if they represent a sample only. Reasons for the low number of women identified with GDM might include the non-universal screening of women for GDM, 'lost' paper-based records, women attending other diabetes antenatal clinics in the region or women treated solely in primary care or general antenatal clinics. It is also likely that a proportion of women who had GDM went undiagnosed due to lower awareness of the condition in the past. Another limitation of this study was the high level of missing data in the paper records for several of the variables of interest which limited our ability to investigate them in depth. Despite these limitations, this is the first study of its kind to be carried out in the UK. The region in which the study was carried out is broadly representative of the total population of

Scotland and the results are more generalizable to the UK than similar studies in Europe and the United States.

Conclusions

In summary, this study clearly shows how a diagnosis of GDM can have an adverse impact on health that extends long after the pregnancy. This study highlights those women with GDM who are at the greatest risk of progressing from GDM to type 2 diabetes and should therefore be prioritised for preventative intervention and suggests there is a viable time window to prevent progression from GDM to type 2 diabetes in the majority of women. While a diagnosis of GDM presents an ideal opportunity for an intervention to reduce the growing burden of type 2 diabetes, identifying the most effective way and optimal time to help women who are at a particularly busy period of their lives to engage in lifestyle change remains a challenge that needs further exploration.

This is the end of the verbatim copy of publication four.

6.6 Critical reflection

The use of data linkage of routinely collected health care data in this study is associated with many of the same strengths and weaknesses that were discussed in relation to publication three and these will not be repeated here. In addition to these, there were weaknesses that related specifically to the methods used in this study. As discussed in the publication, data about women with GDM were extracted by hand by two researchers. Although a standard form was used by both researchers, there is the risk of human error in the transfer of paper records to electronic forms. On reflection, this risk could have been mitigated by having each researcher check a selection of the other researcher's electronic against the paper records. Alternatively, each researcher could have independently carried out data collection for a proportion of the other researcher's records. Comparison of data collection by each researcher would have allowed errors to be identified and helped to ensure consistency in the way data were coded. However, extraction of data from the paper records was very time consuming, taking two researchers six full days to complete. Having a proportion of records being checked by a second researcher would therefore not have been feasible with the resources available for

the study but this is something I will endeavour to incorporate in to future projects where appropriate.

Other limitations associated with the use of paper based records included incomplete and missing data. A number of years of forms had been lost which narrowed down the range of data available for the study. The records were completed by NHS staff for clinical purposes and as a result data were not always complete; for example, data on BMI was not recorded for the majority of women in paper based records. Data from the SMR02 dataset which was linked with data from the paper based records was also not complete for BMI but was nearly complete for SIMD. As discussed in the publication above, the incomplete and missing data in this study was one factor that was likely to have contributed to the fact that this study did not identify all women with GDM. Despite this, it provides a useful overview of the number of women who can be expected to be identified in routine health care practice in Scotland. Having an understanding of this is vital if interventions for women with GDM are to be embedded within routine health care without additional screening being conducted.

In addition to these methodological weaknesses, there are aspects of the reporting in the published paper that could have been clearer or covered in more depth. For example, the paper does not state that the SIMD quintiles used in the analysis were based on Tayside cut-points, rather than Scottish cut points nor how this study population compares to the population of Tayside in terms of SIMD. The study population in paper four were more deprived compared to the whole population of Tayside which would be expected as research in Scotland has shown that higher deprivation according to SIMD is associated with increased risk of GDM (Collier et al. 2017).

Ethical considerations

The methods used in this study are associated with many of the same ethical issues that were discussed in relation to publication three and these will not be repeated here. Ethical issues that related specifically to the methods used in this study included the risk of breach of patient confidentiality as the data extracted on women with GDM contained identifiable information. However, several measures were taken to minimise this risk. Firstly, the patient records and extracted data were not removed from the department they were stored in at Ninewells Hospital. This reduced the risk that the records could be

misplaced or viewed by anyone other than the researchers or staff at the department who would normally have access to the information. Secondly, data were extracted onto an NHS encrypted computer and then encrypted before being sent to HIC. Encrypting the data in this way ensured that only the appropriate individuals at HIC were able to view the extracted data. Identifiable data was only handled for the minimum time possible and only necessary identifiable information was extracted (i.e. only the information required by HIC to link to other datasets). Caldicott principles were adhered to at all times when dealing with identifiable information (National Data Guardian 2016). HIC anonymised the extracted data and this anonymised dataset was used in analyses. The anonymised dataset was stored on a secure server controlled by HIC and accessed according to HIC Standard Operating Procedure (2016), as discussed in relation to the data in publication three.

Chapter seven: Postnatal experiences, knowledge and perceptions of women with gestational diabetes (publication five)

Eades, C., France, E. and Evans, J.M.M. (2018) Postnatal experiences, knowledge and perceptions of women with gestational diabetes. *Diabetic Medicine, 35* (4), pp. 519-529.

This paper was published in Diabetic Medicine, a peer reviewed journal with an impact factor of 3.05. It is the official journal of the charity Diabetes UK and publishes a range of diabetes research of interest to both clinicians and researchers worldwide.

The content of the above publication is presented in this chapter followed by a section providing a critical reflection of the methods. A PDF of the published manuscript can be found in appendix 10. Ethical approval was obtained from both the East of Scotland Research Ethics Committee and the School of Nursing, Midwifery and Health at the University of Stirling (see appendices 11 and 12 for approval letters) and Research and Development approval was gained from NHS Forth Valley (see appendix 13 for approval letter). Informed consent was obtained from each participant to ensure participant understanding of the study and to allow an opportunity for participants to decline to take part in the research (see appendices 14 and 15 for consent for and information sheet respectively).

A verbatim copy of publication five starts below.

7.1 Abstract

Aim

Women with gestational diabetes mellitus (GDM) are at increased risk of type 2 diabetes. This study aimed to explore experiences, knowledge and perceptions of women with GDM to inform the design of interventions to prevent or delay type 2 diabetes.

Methods

Semi-structured interviews were carried out with 16 women with GDM who were recruited from a clinic in one Scottish health board. A framework approach was used to manage and analyse data according to themes informed by psychological theory (self regulation model and theory of planned behaviour).

Results

GDM is not seen as an important, or even real diagnosis among some women, and this perception may result from perceived minimal impact of GDM on their lives. Some women did experience a bigger emotional and practical impact. Knowledge and understanding of type 2 diabetes was poor in general and many women were unconcerned about their future risk. Lower concern appeared to be linked to lower perceived impact of GDM. Lifestyle changes discussed by women mostly related to diet and were motivated primarily by concern for their baby's health. Many women did not maintain these changes postnatally, reporting significant barriers.

Conclusions

This study has suggested potential avenues to be explored in terms of content, timing and potential recipients of interventions. Educational interventions postnatally could address illness perceptions in women with GDM and redress the situation where lack of aftercare downplays its seriousness. For lifestyle interventions, the child's health could be used as a motivator within the context of later joint or family interventions.

7.2 Introduction

Women with gestational diabetes mellitus (GDM) are at a particularly increased risk of developing type 2 diabetes. GDM affects around 5% of pregnancies in Europe (Eades et al. 2016). In women with GDM, normal glucose regulation usually returns shortly after delivery, but these women have up to a seven-fold increased risk of type 2 diabetes compared to women who have not had GDM (Bellamy et al. 2009). Lifestyle interventions targeted at high risk individuals can prevent or delay the onset of type 2 diabetes (Gillies et al. 2007). However, the evidence for interventions that specifically target women with prior GDM is not as compelling (Gilinsky et al. 2015) and many studies report difficulties in recruiting and retaining participants (Cheung et al. 2011).

The challenges facing women with GDM in making lifestyle changes are potentially quite different to those facing other high-risk patient groups (e.g. people with impaired glucose regulation). Learning about the experiences of women with GDM may help to identify whether and which common beliefs and perceptions might be a barrier (or facilitator) to behaviour change, and to help ensure that interventions are appropriately tailored to them. This is important because uptake and engagement with such interventions can be compromised if insufficient attention is paid to the values and concerns of the intended recipients.

There has been relatively little research in the UK exploring the perceptions of women with GDM about this condition and their future risk of type 2 diabetes. Although there has been a meta-synthesis of 16 studies on this topic (Parsons et al. 2014), only one study is UK-based (Lie et al. 2013). The studies have shown that some women have awareness of their increased type 2 diabetes risk, but lifestyle changes that are made during pregnancy are difficult to maintain in the longer-term (Lie et al. 2013). Clearer information is needed, and interventions required that are tailored to women as patients, but also as caregivers (Parsons et al. 2014).

The Medical Research Council (MRC) guidance on developing complex interventions suggests that an appropriate theoretical basis should be identified at the earliest stages of intervention development (MRC 2006). It is argued that the use of theory in intervention design increases the likelihood that an intervention will be effective by ensuring that the causal determinants of behaviour are understood and addressed (Michie et al. 2008). The overall aim of this study was therefore to explore qualitatively the perceptions and experiences of women with GDM in Scotland surrounding their diagnosis, their future risk of type 2 diabetes and preventative lifestyle behaviour, and to identify implications for the development of potential interventions to reduce subsequent type 2 diabetes risk.

7.3 Methods

Theoretical framework

This study was framed by a theoretical approach which combined both the Self Regulation Model (SRM; Leventhal et al. 1992) and the Theory of Planned Behaviour (TPB; Ajzen 1991). The SRM (Leventhal et al. 1992) focuses on patients' beliefs about their health condition and proposes that people interpret information about a potential

illness to create a 'lay' view or representation of the illness. The coping responses then employed (e.g. adhering to treatment regimens or attending appointments), are related to the illness representations the individual holds and to their appraisal of how successful they perceive chosen coping responses to be. These illness representations are formed around seven different themes: identity (label or diagnosis of illness); cause (factors believed to have caused the illness); timeline (expected duration of illness); consequences (expected effects of illness on physical, social and psychological well-being); control/cure (extent to which illness can be controlled/cured); emotional representations (emotional responses to an illness); and illness coherence (how well the person understands their illness).

The TPB (Ajzen 1991) is concerned with beliefs about lifestyle behaviours and asserts that voluntary behaviours are largely predicted by our intentions regarding the behaviour. Intentions, in turn, are determined by our attitude towards the behaviour (our judgement of whether the behaviour is a good thing to do), subjective norms (our judgement of what important others think of the behaviour), and perceived behavioural control (our expectation of how successful we will be in carrying out the behaviour).

These psychological models have been widely used to understand a wide range of health behaviours and because there was no clear evidence to suggest which approach might be most appropriate in the context of the questions posed by our study (Armitage and Conner 2001; Hagger and Orbell 2003), both models were used to underpin our theoretical approach.

Participants and recruitment

Women were recruited from a diabetes antenatal clinic operating in a single Health Board in Scotland, UK. They were eligible if they were aged 18 years and over, spoke fluent English and had been diagnosed in their current pregnancy with GDM according to the Scottish Intercollegiate Guidelines Network guidance (SIGN 2014). Clinical staff identified 49 eligible women from hospital records, gave them information about the study at the clinic and then asked if they were willing for the researcher (CE) to receive their contact details; all women agreed. A convenience sampling approach was used (Coyne 1997). Interested women either gave their details directly to CE (if she was present) or details were given to CE via clinical staff. The women then received an

information sheet about the study and informed that they would potentially be contacted from 8 weeks after delivery. The plan was to conduct approximately 20 interviews, so not all women would be interviewed, and CE collected more names than necessary to allow for drop out. During a post-delivery telephone call, CE checked if the woman was still willing to participate, then scheduled an interview. She had therefore either met or spoken by telephone to every participant before data collection. The final sample size was determined by data saturation, whereby CE conducted interviews until it was felt that no new ideas were being offered by participants.

7.4 Data collection

Attempts were made to contact 31 of 49 women post-delivery; women were selected to achieve maximum variation in factors such as age, parity, ethnicity and BMI. Thirteen women could not be reached using the telephone number held by the researcher and two stated they no longer wished to take part. The remaining 16 women were interviewed between January 2015 and August 2017 (Table 14). All interviews were conducted within a year of the women's due date; the majority (14) between 12 and 26 weeks afterwards. Interviews took place in participants' homes and were carried out by CE (then a part-time PhD student and a registered health psychologist) with previous experience of qualitative fieldwork. The only other individuals present were the baby, or occasionally other children. Participants knew that CE was conducting the study as part of her research degree and that she was not a member of clinical staff but was simply interested in finding out their thoughts on the topic. They were also told that there were no right or wrong answers.

The semi-structured format following an interview guide informed by underlying theory, ensured that the topics of interest were covered while allowing interviewees the freedom to discuss any issues not covered in the guide. The main topics covered were: experiences of diagnosis of GDM; feelings about GDM diagnosis; consequences of GDM; understanding of GDM and information given by healthcare staff; understanding of type 2 diabetes and information given by healthcare staff. Only if it was clear that the participant was already aware of increased risk of type 2 diabetes, were the following topics also discussed: understanding of type 2 diabetes prevention; lifestyle changes for type 2 diabetes prevention; advantages and disadvantages of making lifestyle changes for

type 2 diabetes prevention; views on receiving support to make lifestyle changes after having GDM.

Table 14: Characteristics of participants

Age	**Number**
20-29	3
30-39	11
>40	2
Parity	
+1	9
+2	5
+3	2
Gestation at diagnosis of GDM	
1st trimester	2
2nd trimester	5
3rd trimester	8
SIMD Deprivation Category	
1 (most deprived)	2
2	2
3	5
4	3
5 (least deprived)	4
Ethnicity	
White	12
Asian	3
Black African	1
Key to Participants Quoted in text	
P1	age 39, not first child, white, middle deprivation
P2	age 42, first child, white, low deprivation
P3	age 39, not first child, white, high deprivation
P4	age 22, first child, white, high deprivation
P5	age 34, first child, not white, high deprivation
P6	age 35, not first child, white, middle deprivation
P7	age 35, not first child, white, low deprivation
P8	age 28, first child, white, low deprivation
P9	age 38, first child, not white, low deprivation
P10	age 33, not first child, not white, middle deprivation
P12	age 38, first child, white, low deprivation
P13	age 45, first child, white, low deprivation
P14	age 32, first child, white, middle deprivation
P15	age 38, first child, not white, low deprivation
P16	age 25, not first child, white, middle deprivation

Interviews were audio-recorded with the participant's permission and transcribed verbatim by a professional transcription service (but not returned to the participants). Interviews lasted between 11 and 66 minutes, and field notes written up afterwards. Written informed consent was obtained from all participants and approval to conduct the study was obtained from a National Health Service (NHS) Research Ethics Committee.

7.5 Data analysis

Fieldwork and analysis were conducted in parallel rather than sequentially. The framework method (Spencer et al. 2014) was used to organise and analyse the data combined with coding in NVivo 11 qualitative data analysis software. The framework method is relatively structured and allows pre-set objectives and reasoning to inform data collection whilst still allowing original contributions from participants. The approach involves researchers familiarising themselves with the interview transcripts, then re-reading them and paraphrasing or labelling any passages they interpret as important. These labels can come from predefined theories or models or can be "open", that is where anything that is relevant from any perspective is labelled. In this study the three authors independently reviewed three transcripts and identified and coded areas of interest using an open approach. This open approach was used for the first few transcripts to ensure that any concepts or themes deriving from the data (as well as from theory) were identified.

The three authors then compared their open coding of the three transcripts and agreed that most of the codes could be organised under subthemes derived from the theoretical concepts of the SRM and the TPB. Subthemes were organised under topic themes including GDM, type 2 diabetes, diet, exercise and reactions to a proposed future GDM intervention. Subthemes included, for example, identity, cause, timeline, consequences, and control (for data about GDM and type 2 diabetes). Additional data-derived subthemes included, for example, education about GDM and risk perceptions related to type 2 diabetes. The full list of themes and subthemes are shown in Table 15.

CE then applied the analytical framework to the remaining transcripts and data were summarised using matrices (Gale et al. 2013). Six separate matrices were created, one for each topic theme. Each column was labelled with a subtheme (except column one which contained a participant identifier and demographic data). Each row represented one participant. In each cell of the matrix, relevant data were summarised and a

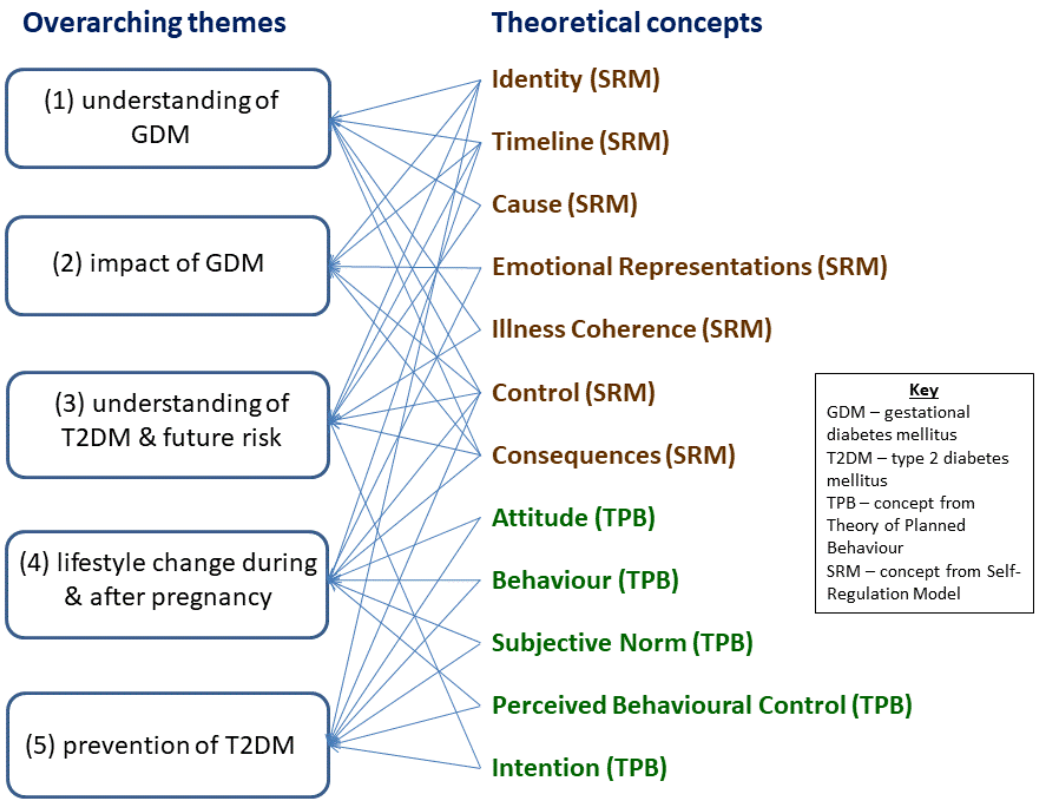
supporting quote given (a matrix excerpt is shown in Appendix 16). A further summary matrix was used to juxtapose each summary of the participants' understanding, and perceived impacts, of GDM and type 2 diabetes. Abstraction and interpretation followed; the matrices were read repeatedly to identify common patterns and disconfirming cases using constant comparison. The findings are presented below as overarching key themes (as depicted in Figure 5).

Table 15: Framework used to organise data

Theme	**Subtheme (theory subtheme relates to)**
1. Background	1.1 Family history[3]
	1.2 Pregnancy experience[3]
	1.3 Previous GDM[3]
	1.4 Postnatal testing[3]
2. Gestational Diabetes Mellitus	2.1 Identity (SRM[1])
	2.2 Timeline (SRM)
	2.3 Cause (SRM)
	2.4 Consequences (SRM)
	2.5 Control (SRM)
	2.6 Emotional Representations (SRM)
	2.7 Illness Coherence (SRM)
	2.8 Education about gestational diabetes[3]
3. Type 2 Diabetes	3.1 Identity (SRM)
	3.2 Timeline (SRM)
	3.3 Cause (SRM)
	3.4 Consequences (SRM)
	3.5 Control (SRM)
	3.6 Emotional Representations (SRM)
	3.7 Illness coherence (SRM)
	3.8 Risk perceptions[3]
	3.9 Prevention[3]
4. Diet	4.1 Attitude (TPB[2])
	4.2 Subjective Norm (TPB)
	4.3 Perceived Behavioural Control (TPB)
	4.4 Intention (TPB)
	4.5 Behaviour (TPB)
5. Exercise	5.1 Attitude (TPB)
	5.2 Subjective Norm (TPB)
	5.3 Perceived Behavioural Control (TPB)
	5.4 Intention (TPB)
	5.5 Behaviour (TPB)
6. Intervention	6.1 Acceptability[3]
	6.2 Ideas[3]

[1]Directly taken from illness representations of the Self Regulation Model (SRM)
[2] Directly taken /mapped to concepts of the Theory of Planned Behaviour (TPB)
[3]Data-derived subthemes

Figure 5: Which theoretical concepts informed the overarching themes



7.6 Results

The results are discussed under the following overarching themes (mapping to key themes two to six): understanding of GDM, impact of GDM, understanding of type 2 diabetes and future risk, lifestyle change during and after pregnancy, prevention of type 2 diabetes. Verbatim quotes from study participants are identified by participant number. Table 14 provides their characteristics.

Understanding of gestational diabetes mellitus

Most women felt they had a good understanding of GDM during their pregnancy. With the time that had elapsed since being diagnosed they struggled to recall specific information about the condition, but most held an overall impression that the information they were given by NHS staff was clear and at an appropriate level. Many praised the staff involved in their care.

"Erm, and they were very good, [the Health Board] were really, really good. I mean it was, it was about an hour and a half, two hours with the diabetic nurse and she went through everything of…and how to use the machine and everything as well." (P9)

When women were less satisfied with the information that they were given, it was generally because this was too vague and not tailored to their specific circumstances, producing feelings of frustration.

"Really to, obviously to eat healthily and exercise but I think the problem is it's very vague as to what eating healthily is." (P7)

"Nobody actually sat down with me and tell me, here's the list of all the food. They gave me a couple of leaflets, erm, but you know, the leaflets is for, erm, you need to customise them based on the patient, what type of food they're used. Because if you're, if you keep telling them, oh don't take, don't have a takeaway, well, I don't have a takeaway, I've already been having healthy eating." (P15)

Although most women explicitly stated that they felt they understood GDM, further discussion revealed areas of confusion or misconception. One was related to the diagnosis of GDM, with some women questioning whether they ever really had the condition. Some suspected that high blood glucose readings identified during diagnostic testing were caused solely by food they had eaten recently, and others felt that a diagnosis very late in pregnancy or one that was classed as borderline meant that the diagnosis was less relevant to them.

"I actually had a big bar of chocolate the day before I went, so I was thinking I bet it's just cause of that." (P8)

"most of what they were telling you wasn't going to really apply to me because I only had, erm, a couple of weeks to go before, erm, I reached my term time." (P6)

These women often rationalised that since they met the diagnostic criteria for GDM they must have had GDM, but still found themselves questioning the diagnosis.

"*So, in one sense you kind of think to yourself, maybe I didnae have it all, and it was just…well obviously I did because I had the fasting thing beforehand"* (P1)

Although not explicitly stated by participants, this questioning of the diagnosis was possibly linked to their perception that GDM had little impact on their lives; many women who questioned their diagnosis did not experience any symptoms, found GDM easy to control through diet, and had blood glucose readings in the normal range during pregnancy and when tested postnatally.

Other common misconceptions related to the causes of GDM. Although some women correctly identified being overweight, family history of type 2 diabetes and ethnicity as risk factors for developing GDM, eating sweet and sugary foods was more commonly understood to have been the cause of this condition.

"I was a sugar person first, yeah, yeah, I liked sugar very much… I said to the person, maybe because I eat sugar too much." (P10).

Impact of gestational diabetes mellitus

Perceptions of how much GDM impacted upon participants' lives varied. We identified three groups of women: women for whom the diagnosis had little emotional impact; those for whom the impact was related to concerns about the wellbeing of their unborn baby; and those for whom the negative emotional impact appeared to last beyond pregnancy. However, the three groups are not necessarily exhaustive or mutually exclusive; this is an emergent finding that needs to be verified.

Women in the first group reported that they were not worried or concerned by the condition at all, with this lack of concern often related to the fact that the condition was relatively common and had little impact on their day to day life.

"it was quite common, so…that sort of puts your mind at ease, it didn't scare me or anything. So, it was okay. Knowing that lots of people get it and it was quite normal…" (P2)

"but if you manage it quite well it's nothing for you, it's like a part of brushing teeth every day, it's like that. You don't even feel like bad that you've got that gestational diabetes; I never felt bad." (P5).

These women explained that the only real consequence of their diagnosis was having to make changes to their diet, which were viewed as being easy to make, and simply

involving cutting out or cutting down sugary foods and drinks; the condition was something temporary that they could forget about after they gave birth.

"No, it's just like a, erm, like buying maternity clothes, and gestational diabetes is like that, and you just forget everything" (P5).

A second group of women had a strong emotional response to being diagnosed with GDM. This was usually caused by worry and guilt that they might have put their unborn baby's health at risk.

"I did, I felt…I actually had a wee cry. I was like, oh, I just felt like I'd let myself down and…maybe I just pigged out [over ate] too much. Um, and just felt as if I'd let her down." (P8)

Often this concern eased after the initial diagnosis as the women learned more about the condition and found that they were able to control and manage it.

"Um, no, to be honest with you, when, when, when I kept checking my sugar levels and that, I just, kind of, thought, well, cannae be that much of a big thing because I'm, I'm not over and I'm not under." (P8)

Less commonly, concern and emotion about being diagnosed with GDM did not lessen over time, and women in the third group reflected that they were still affected by their diagnosis now. These women had often had a much more difficult time in controlling the condition, requiring dietary control to be supplemented with insulin and medication (something which many women stated being reluctant to do). They reported it as time consuming, they found injecting unpleasant and they suffered side effects from the medication.

"So, um, I ended up having to take insulin, which was horrible as well…because they're a needle again. So then I'm testing myself three times a day and my insulin at night, oh, it was just horrible." (P16)

Understanding of type 2 diabetes and future risk

General understanding of type 2 diabetes was very poor. A lack of understanding around types of diabetes and the differences between them was widespread, with many women unable to name type 2 diabetes, and knowing little about it. Some women did identify

poor diet and overweight as risk factors for type 2 diabetes and knew that it is controlled through diet and/or medication; but very few mentioned the health consequences of type 2 diabetes and those who did were very vague about these.

"And obviously there's other health stuff as well at the back of it" (P1)

There were some misconceptions over the causes of type 2 diabetes and its severity. Some women who had older relatives with type 2 diabetes believed it was a consequence of older age; others downplayed its seriousness, especially when they held a preconception that type 2 diabetes had little impact.

"So, it's only type two so it's...I suppose, it's not as bad but" (P4)

"Erm, but my partner's mum she's got type two diabetes and I know that she takes a tablet. I'm sure it's in the morning. And that does her throughout the day" (P4)

Nearly all women recalled being told that they were at an increased risk of diabetes in the future as a result of having had GDM (although few understood the time frame), and that they could reduce their risk through changes to their diet and physical activity levels.

"Maybe not this early and this quick after having them…but probably more than likely later on in life, like maybe when I'm 50, 60, they said that I'll probably, I'll probably be likely to have it, yeah." (P16)

However, many women downplayed the risk for themselves, indicating that because they were not overweight or had no other health problems, or because they had a late diagnosis during pregnancy, this meant that their risk was lower than for other women.

"I have to go every year now for blood tests because of it and I do think it's pretty pointless to be perfectly honest because I think if it hadn't been diagnosed, then they would never have been none the wiser. I don't think it's something that I need to worry about in the future to be honest." (P6)

"she has taken my three-day result, or something, and she took my blood as well on that day, and she counted. And she said ……..you're not that much, er, risk of getting type 2 diabetes. So I thought, okay, that's fine." (P5).

The extent to which women felt concerned by their increased risk of type 2 diabetes varied, but overall concern was not high. Many women made no mention of being worried about their risk of type 2 diabetes and one group of women felt that any risk was far in the future.

"it's not an immediate thing for me, I'm not that fussed about it just now." (P9)

However, one participant had a difficult time managing her GDM when pregnant and felt that it had quite a big impact on her day to day life, as did another participant who reported being concerned about her future risk of type 2 diabetes. This suggests that concern about future risk type 2 diabetes may be linked to more severe perceived or actual impact of GDM.

"I really would hate to be…to get diabetes again. It's horrible" (P3)

Lifestyle change during and after pregnancy

Lifestyle changes discussed in the interviews predominantly related to changes to diet rather than physical activity. Women commonly described cutting out sweet foods, fizzy drinks and other junk food in response to their GDM diagnosis, after initially having been 'eating for two'.

"I say, for me it was just cutting back on eating cakes and chocolates, which is what I'd been having…being pregnant" (P7)

The dietary changes that women made after a GDM diagnosis were most commonly motivated by their concern for the health of their unborn baby and also by a desire to avoid taking medication to manage their GDM.

" just thought of the baby and…obviously I didn't want her to be in any danger when she was, when I was having her or anything like that, any complications or anything like that, so it had to be done." (P8)

"changed my diet just to, kind of, make sure that...because I didn't...I really didn't want to have any, kind of, medication whether it was tablet or, eh, like injection" (P4)

A few women did manage to continue with these changes postnatally, and were currently attending commercial weight loss groups, but most had not managed to maintain the

changes. Once the above motivations had passed, looking after their own health postnatally was not a priority for some women, especially in the face of many new challenges.

"No, but you, you just need to find some energy sometimes. And eating seems to be the right plan for that, but it never is. You just, you know, the sleep deprivation, and, erm, the constant, kind of, needing to be someone else's...you don't really look after yourself so much." (P13)

Changes to physical activity levels were less commonly discussed by participants in this study. Some women recalled being advised to increase their activity levels when they were diagnosed (although this advice was briefer and more peripheral to the education they received on diet), while others did not receive any such advice. There was therefore confusion over what was appropriate.

"I mean exercise, like I said, do more exercise. Walking, jogging, it…what kind of, you know, what, what would prevent it? So no, they didn't really… It was just like do some more exercise and stuff, yeah." (P9)

Among those who did increase physical activity levels, walking, then swimming, were the activities most frequently mentioned. Some women who had previously been active managed to continue this activity during their pregnancy while others reported that they reduced or stopped this exercise during pregnancy. Barriers included having a bump and feeling heavily pregnant, pregnancy-related back and pelvic pain, the demands of having one or more children to look after, tiredness and poor weather.

"where exactly am I meant to go and how am I meant to do this, when I can't nip out to the gym, I can't go and walk the dog, or I can't nip out and see a friend 'cause she's in bed" (P1)

Prevention of type 2 diabetes

The majority of women stated that they would be open to additional support to make lifestyle changes after giving birth. However, two women stated clearly that they would not be interested, while another felt that there was already support available. Among those women who welcomed the idea there was a feeling of being left on their own after the high level of care they had received when they had GDM.

“Um, yeah, I would have…probably…looking back on it now, um, I’d have maybe liked a wee bit more, like, sort of, closure on it, a wee bit more explanation” (P12)

While some women were invited to attend postnatal testing to ensure that their blood sugar levels had returned to normal, others reported that they had to arrange this testing themselves. This lack of aftercare led some women to question how serious their increased risk of type 2 diabetes was.

"But because there's nothing…no after care as such…then you know, it's not like a major thing." (P9)

These women felt that a greater level of aftercare might help to increase their motivation to make lifestyle changes to reduce their type 2 diabetes risk. Some suggested that additional blood testing over the longer term would be beneficial. One woman who was awaiting the results of her postnatal testing described how going for this test had made her think more consciously about her lifestyle.

"when I had the letter through for to say for to go, em, for to get tested, and then you start to think, aah, oh wait a wee minute…and then have I really been paying attention or have I not …I know this sounds terrible, but in one sense I’m hoping it comes back quite high to give myself sort of a kick in the bum, do you know what I mean." (P1)

As previously discussed, some women felt a need for more specific information about making changes to their lifestyle and suggested that this could be tied in with going for postnatal blood testing. Other women felt that group support to make lifestyle changes that involved other mums would be most beneficial for them.

“As much as I love my mum, not just your mum going…you’re doing well and you’ve lost a wee bit of weight, well done and it took me so long after I’d had babies and stuff, but girls that are going through it…that are exactly the same as you. And that’s been a really good support network…” (P2)

Women who lived outside the main towns/cities in the health board also noted that there were fewer group activities available to them.

7.7 Discussion

This study provides an understanding of women's perceptions and experiences of GDM, of making lifestyle changes after a diagnosis of GDM and their risk perceptions about type 2 diabetes. In general, most women in this Scottish study had a positive experience of health care after their GDM diagnosis, as reported elsewhere in the UK (Lie et al. 2013), but in contrast to the findings from a synthesis of international qualitative studies (Parsons et al. 2014). However, women identified an explicit need for more specific dietary advice, and advice on physical activity, during pregnancy and in the postnatal period.

While the transitory nature of GDM was emphasised by some women in this, and other studies (Parsons et al. 2014), the belief that GDM is not an important (or even real) diagnosis, has not previously been explored, and often occurred among women for whom the perceived impact of GDM was minimal. Similarly, while most women had some (often vague) awareness of their future type 2 diabetes risk (confirming previous studies Parsons et al. 2014; Lie et al. 2013), a lack of concern appeared to tie in again with a minimal perceived impact of GDM. This is an important group of women to identify and target for preventative intervention, so that they understand the importance of behaviour change even if their GDM diagnosis did not seem significant at the time.

The perception among some women that GDM was an insignificant diagnosis without longer-term implications, was reinforced by the perceived lack of after care and follow-up. If such follow-up were provided, this might act to counter the postnatal resolution of GDM 'lulling women into complacency' (Parsons et al. 2014).

Many women did achieve dietary and/or exercise behaviour change during pregnancy, and this was often motivated primarily by concern for their baby's health. This ties in with the worry and guilt that increased the emotional impact of GDM among some women. However, awareness of type 2 diabetes risk did not provide sufficient motivation to overcome barriers to lifestyle change postnatally (including tiredness, lack of energy and the demands of a new baby).

The strengths of this study include the participation of women with a range of different demographic characteristics such as age, ethnicity, and deprivation. By using theoretical models to inform the design and analysis, we have highlighted a range of beliefs and

illness perceptions which impact upon lifestyle change both during and after pregnancy. The sample size was relatively small and all women were recruited from one health board; this may mean that the experiences of care that women reported may not be comparable to women in other geographical areas. It was also only possible to ask questions about women's views surrounding type 2 diabetes once they had indicated that they were already aware of their increased type 2 diabetes risk. While this may have introduced a slight bias, it was a requirement stipulated for ethical reasons, in order that women were not distressed by their sudden realisation of longer-term and more serious consequences of GDM. While we ensured that a selection of transcripts were coded independently by all three authors and the framework was developed through discussion between them to allow for varied and richer interpretations of the data, it is still possible that this study was influenced by the researchers' backgrounds and beliefs. Despite these limitations, our findings accord and build upon those from a previous UK study (Lie et al. 2013).

Findings for this study have important implications for the development of potential interventions for women who have had GDM. Regarding educational interventions, given the perception of GDM as being short-lived, easily controlled and having few consequences, this study suggests that illness perceptions surrounding GDM (as defined in the SRM), particularly the 'consequences', need to be addressed; and would be appropriately aimed at women for whom the perceived impact of GDM was minimal. The 'timeline' and 'consequences' of type 2 diabetes are also poorly understood and could be tackled. Timing such an educational intervention soon after delivery, combined with longer-term follow-up and testing, would help to redress the situation where a current lack of aftercare downplays the seriousness of GDM and subsequent type 2 diabetes risk.

In terms of lifestyle interventions for behaviour change, it is clear that women feel the need for more specific dietary and physical activity advice. There are significant barriers to behaviour change with a young family (perceived behavioural control in the TPB). However, given that the health of their unborn baby facilitates behaviour change during pregnancy, it may be that an important later source of motivation could be their child's health, which could be used to target behavioural attitudes and intentions within the context of a joint or family intervention. Although other studies have identified weaning

as a time of increased receptiveness to lifestyle change (Parsons et al. 2014), this logic could extend to other times during a child's development.

In summary, this qualitative research with women about their experiences of GDM, underpinned by psychological theory, has suggested potential avenues to be explored further in terms of content, timing and potential recipients of interventions to reduce the risk of type 2 diabetes in women who have had GDM.

This is the end of the verbatim copy of publication five.

7.8 Critical reflection

The concepts of reliability and validity are central to the critical analysis of scientific research and are concerned with the credibility of research evidence (Lewis et al. 2014). Validity refers to the extent to which the findings accurately measure the phenomenon under study and reliability to the how replicable the findings of the study are, i.e. would the findings be consistent if the study was repeated? These concepts were developed in relation to quantitative research findings and their application to qualitative research has been the subject of much debate. It has been argued that differences in the philosophical underpinnings of quantitative and qualitative research, as discussed in chapter three, mean that reliability and validity have limited value in qualitative research (Noble and Smith 2015).

Lincoln and Guba (1985) proposed the following four criteria for assessing the trustworthiness of qualitative research as an alternative to reliability and validity: credibility, transferability, dependability and confirmability. The concept of credibility is analogous to internal validity and considers how congruent the findings of the research are with reality. Transferability is similar to the concept of external validity and refers to the extent to which findings can be generalised to wider populations. Dependability in qualitative research is proposed in preference to the concept of reliability. Confirmability in qualitative research is comparable to the concept of objectivity in quantitative research and refers to the extent to which the findings of the study are affected by researcher bias (Shenton 2004).

The lack of consensus on how to assess the quality of qualitative research can make it difficult for researchers to demonstrate the credibility of their findings and can lead to the

research being deemed as lacking rigour and transparency (Mays and Pope 1995). Regardless of the terminology or approach used, it is important that researchers attempt to address quality in qualitative research to avoid these potential criticisms. A number of strategies can be used to address the trustworthiness of qualitative research findings with some of the most commonly used being triangulation, respondent validation, peer scrutiny of research, clear exposition of methods and reflexivity (Mays and Pope, 1995; Noble and Smith 2015). Each of these strategies will be discussed below with reference to the present study's strength and weaknesses. Finally, the ethical issues associated with this study will be considered.

Triangulation

Triangulation is where a researcher uses more than one method of data collection or source of data to answer a research question. Results from these different methods are compared with the aim of confirming or providing a more comprehensive understanding of the findings (Mays and Pope 2000). Barbour (2001) argues that although triangulation appears easily achievable, it is difficult to carry out correctly in practice. Data from qualitative and quantitative methods are in different forms making direct comparison difficult. Data from different qualitative methods, for example interviews and direct observation, can also be difficult to compare directly. Barbour (2001) suggest that although similar findings arising from triangulation provide reassurance, an absence of similar findings does not necessarily call in to question the validity or credibility of the finding. Mays and Pope (2000) suggest that rather being used as a measure of credibility, triangulation is better viewed as a way of ensuring that research is as comprehensive as possible. Triangulation was not carried as part of the present study but since this study was conducted I have been involved in a further study using the framework developed in the present study. This study applied the framework to forum posts mentioning gestational diabetes from websites for parents: mumsnet and netmums. The study is not yet complete but preliminary findings are consistent with publication five. Posts on the forums by women with gestational diabetes were largely related to concerns about the health of their baby, fears about delivery of a potentially large baby, and very rarely mentioning their future risk of type 2 diabetes (Evans 2018). Women posting on these forums generally do not post using their real names and so may arguably be less subject to social desirability bias than in a face to face interview with a researcher. The consistency of Evans (2018) findings with those in publication five therefore suggests

that women's responses in publication five were not a result of social desirability bias (where participants give responses that they believe to be socially desirable; Paulhus 1991) or demand characteristics (where participants responds in a way that they believe the researcher wishes them to; Orne 1962).

Respondent validation

Respondent validation is a technique that aims to increase the credibility of qualitative findings and involves the researcher checking interim research findings with the participants themselves. By using this technique, the researcher can establish whether the interpretations they have made are appropriate and supported by participants (Mays and Pope 2000). Although this approach has value in ensuring the credibility of research findings it has limitations and may not always be appropriate (Barbour 2001). The overview of findings produced by the researcher is designed for a wide audience and as such may not reflect an individual's concerns or focus and lead to discrepancies (Mays and Pope 2000). Respondent validation also places demands upon the participant's time. As participants in the present study had young babies it was felt that it would not be appropriate to place further demands on their time by asking them to review and comment on study findings.

Peer scrutiny

Although participants' views on the research findings were not sought, peer scrutiny was incorporated at various points in the present study. Other researchers were involved in the analysis of the findings through the use of multiple coding of transcripts. Multiple coding of transcripts refers to the process by which researchers independently code transcripts and then compare the codes applied. Multiple coding was only carried out on a selection of transcripts, rather than the whole dataset, and we did not calculate the degree of concordance between researchers. However, Barbour (2001) argues against multiple coding of entire datasets due the cost and time implications of this and suggests that it is not the specific degree of concordance that is important, but rather the process of multiple coding itself that improves rigour. Having other researchers from different backgrounds carry out multiple coding was valuable in helping me to challenge the assumptions I made and offered different perspectives on the data. This was important in ensuring the credibility of the research and also in helping to reduce researcher bias.

In addition to multiple coding, I presented a summary of emerging codes/themes at an early stage of the analysis to clinicians involved in the care of women with GDM in the local health board (consultants and diabetes specialist nurses) and sought their views on my interpretations. Although I intended this study to be informed by psychological theory, having other researchers and clinicians from different backgrounds helped to ensure that I considered alternative explanations not offered by these theories.

Exposition of methods and findings

Clear description of methods and findings is an important strategy in addressing the quality of qualitative research and can assist readers in assessing the generalisability or transferability of the findings. The concept of generalisability is particularly problematic in qualitative research as samples are not gathered with the intention of the findings being generalised to other populations (Shenton 2004).

There were a number of characteristics of the present study which may have affected the transferability of the findings. Firstly, the sample was small and recruited from only one health board in Scotland. Women who took part in the study were all attending a clinic for management of their GDM. It could therefore be argued that these women were more concerned about managing their condition than women who did not attend the clinic. However, clinical staff reported that non-attendance rates at this clinic were very low which suggests that the women we had access to were quite typical of all women in the health board diagnosed with GDM. Recruiting from only one health board may have limited the transferability of the findings as women in different health boards are likely to have had different experiences of having GDM, and of the care they received for this. However, clinicians used national guidance for treating and managing GDM.

Despite the difficulties in generalising from qualitative research, Lincoln and Guba (1985) suggest that if researchers provide contextual information about a study and where it was conducted, then readers can make judgements themselves about the transferability to other contexts. In this study, the COREQ checklist (Tong et al. 2007) for reporting of qualitative interview findings was used when preparing the written report of the study. A completed copy of this checklist can be found for the present study in appendix 17. All relevant items in the COREQ checklist were reported in the published report of the

present study. By providing this information, readers can make judgements about the transferability of the findings of publication five to their own context.

Reflexivity

Reflexivity be defined as the process of evaluating our own position and background as the researcher and the effect that this might have on our research (Berger 2015). Reflexivity is an important strategy for reducing the effects of researcher bias and strengthening the confirmability of the study. In addition to having multiple investigators involved in the research process, as discussed above, other steps that were taken to foster reflexivity in the present study included reporting my background and position in the published report of the research and keeping a reflective journal. As part of the field notes taken during the data collection and analysis I recorded my thoughts on how data collection was progressing, the decisions I made and the reasons for these decisions. In these notes I reflected on how my own values, beliefs and professional background as a Health Psychologist might influence the research process.

In addition to professional background, other researcher characteristics that can influence the research process include sex, sexuality, age, race, personal experiences, political ideologies and immigration status among others (Berger 2015). Berger (2015) suggests that these factors can affect the research in three ways. Firstly, they can influence the access that the researcher has to the study field as people may be more willing to engage in research if they perceive the researcher to be like them or sympathetic to their situation. Secondly, the characteristics of the researcher can affect the information that a participant is willing to share with the researcher, and thirdly, they can influence the way that the researcher interprets what a participant is saying, the way they pose questions and how they analyse the findings.

Of the factors discussed it would seem likely that sex of the researcher and personal experiences of pregnancy and gestational diabetes would be of most relevance in the present study. I was pregnant in the later stages of data collection for this study and during my pregnancy I underwent the same testing for gestational diabetes as women in this study. It is possible that these factors may have made women more willing to take part in the study and influenced the information they were willing to share with me. However, prior to me being visibly pregnant I found that most women didn't ask me if I had

children, and in my field notes I recorded that women seemed comfortable talking to me about personal and sensitive aspects of their pregnancy both before and after my pregnancy. The proportion of women agreeing to be contacted after they gave birth was very high throughout the study and did not change over time. Similarly, the proportion of these women who were contactable and agreed to take part when followed up after giving birth remained stable over the course of the study. Therefore, it seems that my changing circumstances during the study period did not seem to affect my access to participants or the information they were willing to share with me. The fact that I was a woman of a similar age to most participants in this study may have been enough to make women feel comfortable sharing personal information with me, regardless of whether I had children or not.

Berger (2015) suggests that there are both advantages and disadvantages to the researcher studying a topic they are not personally familiar with. Being unfamiliar with the topic can help to reduce the power imbalance between the researcher and the participant as the participant can take the role of the expert. At the beginning of all interviews I made it clear to participants that I was not an expert on the topic but was there to listen to their views and experiences. On the other hand, challenges of carrying out research on a topic that you do not have personal experience of include that researchers may not be able to fully comprehend what it is like to experience the situation being described by participants and may struggle to recognise some of the nuances in the language of the topic they are studying. This in turn can affect the researcher's ability to form appropriate questions and follow these up with suitable probes. My reflections recorded in my field notes were consistent with this as I noted how being pregnant gave me a better understanding of the challenges of pregnancy and how it influences behaviour and emotions, which in turn helped me to empathise with women and explore this aspect in more detail. For example, having experienced testing for gestational diabetes I understood more about the practical difficulties of attending this test that some women discussed, and experienced some anxiety about the results of the test. I also appreciated some of the challenges of making lifestyle changes, particularly in relation to physical activity, when suffering common pregnancy complications like morning sickness and pelvic pain. Furthermore, after my pregnancy I felt I had a clearer understanding of the clinical care that women received in pregnancy and the terminology associated with this.

However, prior to being pregnant I would ask women to clarify anything I didn't understand and I think that this is unlikely to have had a large impact on the research.

It is not possible to avoid researcher subjectivity entirely in qualitative research but by taking steps to encourage reflexivity throughout the research process I have a better understanding and awareness of how my own position as the researcher influences my research. Some authors argue that the unique position of the researcher can add value to qualitative research, and in the present study I feel that the changes in my position and circumstances had a positive influence on my engagement with participants and the data. Although some aspects of my background and position as the researcher were discussed in the published report of this paper, limited space meant it was not possible to do this in depth which might be considered a weakness of this paper.

Ethical considerations

Face to face interviews are associated with a number of potential risks to both the participants and the researcher. The main ethical issue in the present study related to the discussion of future risk of type 2 diabetes with participants and the possibility that patients would not be aware of their own increased risk. Interviews were conducted approximately eight weeks after birth meaning that women would have attended their six week postnatal check-up by the time interviews are conducted. I was informed by the clinical staff involved in the study that all women would be told about their increased risk of type 2 diabetes at this six week check-up. However, I also understood that some women did not attend this check-up and therefore may have been unaware of their increased risk. There was also the possibility that women who did attend may not fully take this information in or remember it. Every effort was made to ensure that women did not discover this information for the first time during the interview. I checked whether the participant had discussed type 2 diabetes with their health care provider or was aware about it from any other source. For any women who were not aware of the link between type 2 diabetes and GDM, the line of questioning around type 2 diabetes and preventative behaviours was not be followed up. Despite this risk I felt it was important to try to discuss perceptions of risk with patients where possible as theory and research both suggest perception of risk may influence on adoption of risk reducing lifestyle behaviours (Janz and Becker 1984).

Even in those women who were aware of their risk of type 2 diabetes, discussing this might have caused distress or worry in participants. Although none of the participants showed any signs of distress, if this had happened I had planned to check that they were willing to continue with the interview and reiterate that they could withdraw from the study at any time. After the interview all participants were offered information about resources where they can find out more about diabetes (e.g. Diabetes UK website) and to a telephone support line where they can discuss any worries they had (the Diabetes UK Care line which is a telephone service where patients can speak to trained counsellors).

Another ethical issue for participants related to the approach taken to recruitment. There was a possibility that women could feel under pressure to agree to give me their contact details at the clinic. However, both myself and the clinical staff highlighted the voluntary nature of participation and explained that by giving contact details they were not agreeing to participate. They were also told that even if they did agree to participate, they were free to withdraw at any point from the study without any consequences to them or their health care. The women had a sufficient period (eight weeks) between receiving information about the study and being contacted by myself to fully take in the written information and think about their participation.

Finally, conducting interviews in the patient's home presented a risk to the researcher. Several steps were taken to reduce this potential risk. I carried a mobile phone and arranged to make contact via text message with an agreed contact at the University of Stirling, both prior to entering the participants home and again when the interview was completed. I also gave this contact a list of the dates and times of interviews and the address I was visiting for each interview.

Chapter eight: Discussion

This chapter will begin by summarising the findings of this thesis and will then consider the importance of these findings and how they compare to other research in this field. The implications of the findings for the development of lifestyle interventions for people with IGR and women with GDM will then be discussed. Finally, recommendations arising from the thesis will be summarised.

8.1 Summary of thesis and findings

This thesis described prevalence estimates, rates of progression and patient perceptions in relation to IGR and GDM: two conditions that put people at a particularly increased risk of type 2 diabetes. The aim is for the body of work in this thesis to inform the development of interventions to prevent or delay progression to type 2 diabetes in these patient groups.

Impaired glucose regulation

Prevalence estimates of IGR in developed Europe were summarised and factors that influenced these estimates were identified by conducting a systematic review and meta-analysis. The meta-analysis reported that more than one in five people in the general adult population of developed Europe met the criteria for either IGT, IFG or both. Mean prevalence of IGT in the general adult population overall was 11.4% and did not differ by gender. Mean prevalence of IFG in the general adult population overall was 8.4% and significantly higher in men at 10.1% compared to 5.9% in women. Sample age, diagnostic criteria and country were found to have a significant univariate effect on prevalence of IGT, but only diagnostic criteria remained significant in multivariate analysis. The only moderator variable with a significant effect on IFG prevalence was country.

This thesis also reported incidence of IGR and progression to type 2 diabetes in the UK in an observational retrospective study using routinely collected health care data. Total incidence of IGR across the study period was 2,720 per 100,000 person years. No significant differences were found in incidence by gender or deprivation category, but incidence was found to increase with increasing age. During the study period 9% of patients with IGR were diagnosed with type 2 diabetes with a mean time of 34 months between IGR and type 2 diabetes diagnosis. At a significantly increased risk of

progression to type 2 diabetes were men, those living in an area of deprivation and older patients.

Gestational diabetes mellitus

Prevalence estimates of GDM in developed Europe were summarised and factors that influenced these estimates were identified by conducting a systematic review and meta-analysis. This meta-analysis reported mean prevalence of GDM in the general population of pregnant women in developed Europe of 5.4%. Maternal age, year of data collection, country, area of Europe, week of gestation at testing, and diagnostic criteria were found to have a significant univariate effect on GDM prevalence with area, week of gestation at testing and year of data collection remaining statistically significant in multivariate analysis.

An observational cohort study using routinely collected healthcare data was carried out in the UK to investigate long term risk of type 2 diabetes in women with GDM. The study found that one quarter of women with GDM developed type 2 diabetes, with a mean time period of eight years between diagnosis of GDM and type 2 diabetes. Increased weight during pregnancy, use of insulin during pregnancy, higher HbA1c levels at diagnosis of GDM and fasting blood glucose were all associated with an increased risk of developing type 2 diabetes after GDM.

Finally, semi-structured interviews were conducted to explore the experiences, knowledge and perceptions of women with GDM. Women who participated in the interviews did not view GDM as something important and perceived it to have minimal impact on their lives. Linked to this, knowledge and understanding of type 2 diabetes was poor and women were unconcerned about their future risk. Changes women made to their lifestyle, largely to diet, were motivated by concern for their baby's health and many women did not maintain these changes postnatally.

8.2 Importance of findings and comparison to existing research

Impaired glucose regulation

Publication one – meta-analysis of impaired glucose regulation prevalence

This publication was the first systematic review and meta-analysis to summarise data on the prevalence of IGR in Europe. Previous research estimating IGR prevalence in Europe has produced widely varying estimates. For example, a study of IGR prevalence in 13 populations across nine European countries reported prevalence estimates of IGR that ranged from 3.2% to 64.2% (DECODE study group 2003). By synthesising all the available research on this topic, publication one provides clarity on what underlies some of the variations in reported prevalence estimates of IGR.

Differences in the diagnostic criteria used to identify IGR have been suggested as one possible reason for the disparity in prevalence estimates in published research. The specific values and types of tests used for diagnosing IGR have changed over time and differ in guidelines published by different organisations. This is particularly true for IFG with considerable differences in the types of test and cut off values recommended by the ADA (2010) and WHO (2006) guidelines. A study comparing these diagnostic criteria in Denmark found the lower diagnostic threshold used by the ADA guidelines resulted in IFG prevalence of 37.6% in the sample compared to prevalence of only 11.8% when WHO criteria were applied (Borch-Johnsen et al. 2004).

Consistent with the findings of the Borch-Johnsen et al. (2004) study, the systematic review and meta-analysis in publication one found that diagnostic criteria had a significant effect on prevalence of IGT. Prevalence of IFG increased when wider criteria were used but these findings were not statistically significant. However, prevalence of IFG was analysed separately by sex meaning that there were only a small number of studies in some of the diagnostic criteria categories; the lack of statistical significance for diagnostic criteria as a moderator of IFG prevalence may therefore be a result of insufficient power in the analysis rather than indicating lack of an effect. The mean prevalence estimate of 22.3% for IGR in the general adult population reported by the meta-analysis is therefore largely consistent with the widely accepted figure of 15% (DECODE study group 2003) when the differences in the criteria these estimates are based upon are considered.

Further difficulties in understanding the research on IGR prevalence arise from inconsistent findings on the demographic factors that influence the distribution of IGR. Prior to the systematic review and meta-analysis conducted as part of this thesis, data from the DECODE study (2003) in 13 European populations was cited as the most robust evidence for differences in IGR prevalence according to age and sex (Unwin et al., 2002). The DECODE study reported that IFG is more common in men than women in all age groups and IGT is more common in women than men in those aged 30-39 and 70-79. Sex differences for IGT were not significant in other age groups. The DECODE study also found that prevalence of IGT increased across all age groups but that IFG plateaued in middle age and decreased in older men (Unwin et al., 2002). Although patterns were identified in the DECODE study according to age and sex, it is important to note that there were differences in findings between the individual populations summarised in the publication and that prior to the DECODE study the impact of sex on IGR prevalence was unresolved (Unwin et al. 2002; DECODE Study Group 2003). The meta-analysis reported in publication one confirmed the trends reported by the DECODE study (2003) of higher prevalence of IFG in men compared with women, and higher prevalence of IGT but not IFG with increasing age. The less robust DECODE finding of higher IGT prevalence in women compared with men in some age groups was not confirmed in this systematic review and meta-analysis. By synthesising all the available literature on this topic using meta-analysis methods, publication one was able to assess the effects of several variables on IGR prevalence at the same time allowing stronger conclusions to be drawn about the importance of these variables in influencing IGR prevalence.

By providing a clear understanding of how many people in the general population are likely to have IGR, and who is more likely to have it, interventions to prevent type 2 diabetes can be planned and appropriately targeted. Publication one is therefore useful not only as a reference paper for researchers writing about this topic, but it also provides a basis for the planning of interventions and health care provision for the prevention of type 2 diabetes.

Publication three – incidence of impaired glucose regulation and progression to type 2 diabetes

The observational retrospective study carried out in publication three was the first study of IGR incidence and progression to type 2 diabetes in the UK. Using routinely collected

health care data allows for incidence to be assessed without the need for costly and time-consuming repeated testing of a sample of people over a period of time although incidence based on health care data may not represent true incidence in the general population (Zimmet, Alberti, Magliano Bennett, 2016). Furthermore, using routinely collected health care data to estimate incidence of IGR offers an approximation of how many people with IGR are currently being identified by the health service. This is important for planning current and future health care delivery and for planning preventative efforts for people with IGR (Zimmet et al. 2016).

Although recent NICE guidelines (2011) on the prevention of type 2 diabetes recommend that GPs and other primary health care health professionals use validated risk assessment tools to identify those who may be at high risk of developing type 2 diabetes, research has suggested that this type of screening is rarely carried out in practice (Noble et al. 2011). The lack of a universal approach to identifying people at high risk of type 2 diabetes in practice makes it particularly important to assess how many people with IGR are currently being identified by the health service in a region if interventions are to be developed for this setting. Publication three reported that a considerable number of patients were identified as having IGR during routine health care in the Tayside Health Board which suggests that it would be feasible to deliver interventions to people with IGR in the health care setting without the need to carry out additional screening.

No studies assessing incidence of IGR were identified by the systematic review in publication one. Although incidence and prevalence are different concepts they are closely related meaning that the findings of the meta-analysis of prevalence and the observational study of incidence can be compared. The incidence rate of a disease can be defined as the frequency of new occurrences of a disease in a population at risk over a period of time (Webb and Bain 2011). In contrast prevalence is the proportion of people who have the disease at a specific point in time. Generally speaking, the prevalence of a disease is equal to the incidence rate multiplied by the average duration of the disease. This assumes a stable population where the number of people entering the population is equal to the number leaving the population (Webb and Bain 2011). As IGR does not have a very short duration we would expect prevalence of IGR to be higher than incidence which is consistent with the findings in the study of incidence in publication three and

meta-analysis of prevalence in publication one. As incidence and prevalence are closely related we would also expect them to be affected by the same demographic factors.

The observational cohort study carried out in publication three reported some trends in IGR incidence that are consistent with the findings of the meta-analysis in publication one. In publication three, incidence of IGR was found to increase with age which is consistent with the meta-analysis but the sex differences in IGR reported in the meta-analysis were not found in publication three for IGR incidence. It was not possible to analyse sex differences in incidence for IGT and IFG separately in publication three because only an FPG test was conducted or recorded for the majority of patients in this study. Although WHO (2006) guidelines state that it is possible for a single elevated FPG to be used to diagnose IFG it also states that this classification is uncertain because a diagnosis of IGT cannot be excluded and thus we were unable to separate cases of IGT and IFG with confidence. Given that sex differences in prevalence were only reported for IFG and not IGT in the meta-analysis it is not surprising that trends for sex were not found in publication three when IGT and IFG were analysed together.

In addition to reporting the number of new cases of IGR identified through routine health care in the UK, publication three was also the first to report progression to type 2 diabetes in Scotland using routinely collected health care data. Understanding rates of progression to type 2 diabetes is important for planning the timescale for delivering interventions to prevent type 2 diabetes. Publication three reported that 9% of patients progressed to type 2 diabetes in a mean time of 34 months over a five year study period. A meta-analysis by Morris et al. (2013) reported that the incidence rate of type 2 diabetes was 4.5% per year in people with IGT and 4.7% per year for IFG. Morris et al. (2013) reported that progression rates differed according to the criteria used to define IGR, but the progression rates reported above were based on WHO criteria (2006) as were the progression rate reported in publication three meaning that these figures should be comparable. Although these figures cannot be directly compared with those reported in publication three as they are expressed as a rate per year and are only for people with IFG, the incidence of type 2 diabetes in publication three is lower than in the Morris et al. (2013) meta-analysis.

The meta-analysis by Morris et al. (2013) summarised studies from across the world including Asia, Europe, North America, Africa and Australia. Trends in type 2 diabetes are known to vary in different regions of the world (WHO 2016). South East Asia and

Western Pacific Region, two areas included in the meta-analysis, have the largest number of people with type 2 diabetes and together account for approximately half of all type 2 diabetes cases worldwide (WHO 2016). Although type 2 diabetes prevalence has risen globally, this rise in prevalence has been faster in low and middle-income countries compared to high income countries (WHO 2016). These differences in type 2 diabetes trends across regions of the world may mean that the summary figures reported by the Morris et al. (2013) meta-analysis are not comparable to the incidence rates reported in publication three which were based on data from Scotland, a high income European country.

Two studies conducted in the UK assessing incidence of type 2 diabetes in people with IGR were included in the Morris et al. (2013) meta-analysis (Wareham et al. 1999; Forouhi et al. 2007) and two further UK studies published after the Morris et al. (2013) review were identified (Gillett et al. 2012; Hong et al. 2016). The Wareham et al. (1999) study assessed incidence of type 2 diabetes in people with HbA1c levels that were raised but not high enough to be diagnostic of type 2 diabetes (Wareham et al. 1999). Although both the ADA (2011) and WHO (2011a) now recommend that HbA1c can be used in the diagnosis of IGR and type 2 diabetes, research has shown that HbA1c and FPG/2hPG tests do not identify the same people as being at high risk of type 2 diabetes (Mann et al. 2010; Barry et al. 2017). Therefore, the findings of the Wareham et al. (1999) study are not comparable with those of publication three.

The second UK study identified by the Morris et al. (2013) meta-analysis was a longitudinal study of a random sample of adults of European origin without type 2 diabetes drawn from one general practice in England (Forouhi et al. 2007). In this study, around one quarter of the 257 participants were found to have IFG at baseline using the same diagnostic criteria as publication three (FPG of 6.1 to 6.9mmol/l). The rate of type 2 diabetes incidence in people with IFG was 1.75% per year over the 10 year study period. Incidence of type 2 diabetes in people with IGR in publication three was 9% over a study period of five years with a mean time of around three years between diagnoses of IGR and type 2 diabetes. Again, the different units of measurement mean that these figures cannot be directly compared but the rate of progression to type 2 diabetes in publication three appears to be reasonably consistent with the rate reported by Forouhi et al. (2007).

The two studies published after the Morris et al. (2013) systematic review both used data from routinely collected electronic health records in the UK (Gillett et al 2012; Hong et al. 2016). The study by Gillett et al. (2012) identified people coded as having IGT or IFG between 2000 and 2005 in the General Practice Research Database: a longitudinal primary care database containing data that covers around 6% of the UK population. In total, 29.3% of the 9,096 people identified as having IGT or IFG in the Gillett et al. (2012) study developed type 2 diabetes over a median follow up of 2.9 years (minimum follow up 0.9 years, maximum 53.6 years) The proportion of people progressing to type 2 diabetes in the Gillett et al. (2012) study was higher than in publication three where 9% of people with IGR developed type 2 diabetes in a mean time of 34 months. Although the mean and median follow up times for the two studies were similar, the maximum follow up period in publication three was much shorter at eight years compared to 53.6 years in the Gillett et al. (2012) study. The shorter follow up in publication three may partly explain the lower proportion of people with IGR who developed type 2 diabetes. The diagnoses of IGT and IFG in the Gillett et al. (2012) study were based on codes recorded in GP records, whereas publication three used blood glucose test results meaning that the findings of the two studies may not be directly comparable.

The study by Hong et al. (2016) used the same diagnostic criteria for identifying IFG (FPG of 6.1 to 6.9mmol/l) as publication three, meaning that the findings are particularly comparable. Incidence of type 2 diabetes in the 49,041 people with IFG who received a subsequent FPG test after diagnosis was 5.86 per 100 person-years. The incidence of type 2 diabetes in people with IGR in publication three was less than half of that in the Hong et al. study (2016) at 2.72 per 100 person-years. However, the Hong et al. study (2016) only included people with a subsequent FPG test after diagnosis of IFG whereas in publication three people were included if they had one blood test meeting the diagnostic criteria. By only including participants with one elevated FPG test publication three may have falsely identified some people as having IFG or IGT when they may in fact have had elevated blood glucose levels for other reasons, such as illness. The possible incorrect identification of IGR in some patients in publication three may have contributed to the lower incidence of type 2 diabetes. Furthermore, Hong et al. (2016) suggested that those patients who receive a subsequent FPG after diagnosis of IGR are likely to be those considered at highest risk by their health care providers and therefore more likely to develop type 2 diabetes.

Publication three also reported that of the people identified as having IGR, those who were older, with IGT, male and living in a more deprived area were at the greatest risk of progressing to type 2 diabetes. Consistent with this, the study by Forouhi et al. (2007) also found higher incidence of type 2 diabetes with increasing age. However, two meta-analyses reported no difference in risk of progression to type 2 diabetes between IGT and IFG (Gerstein et al. 2007; Morris et al. 2013). Because the majority of instances of blood glucose results in publication three were from a single test fasting only, it was not possible to be certain of the classification of IFG and IGT. As these classifications are not certain the findings regarding IGT and risk of progression need to be interpreted with caution.

Research exploring the influences of a person's sex on the risk of progression to type 2 diabetes has produced mixed findings. Consistent with publication three, Forouhi et al. (2007) reported higher incidence of type 2 diabetes in men with IFG than in women whereas other research reported no difference between sexes (Qiao et al. 2003; Hong et al. 2016). The meta-analysis by Gerstein et al. (2007) reported that there was insufficient data to allow the effect of sex on progression to type 2 diabetes to be explored. No studies were identified that assessed the effect of deprivation on progression from IGR to type 2 diabetes. The influence of sex and deprivation on incidence of type 2 diabetes in people with IGR are therefore areas that would benefit from further investigation.

The findings of publication three are generally consistent with and build upon the small body of literature assessing progression from IGR to type 2 diabetes in the UK. Publication three provides an understanding of the incidence of type 2 diabetes and the timescale of this in patients identified as having IGR through routine health care delivery in Scotland. As such it provides important information for planning interventions and health care delivery with this group of patients in this region.

Gestational diabetes mellitus

Publication two – meta-analysis of gestational diabetes mellitus prevalence

Although narrative literature reviews exist summarising GDM prevalence in Europe, this thesis reports the first systematic review and meta-analysis to bring together all the evidence on this topic. Estimating prevalence of GDM has been challenging as rates vary from study to study due to a lack of accepted diagnostic criteria. The ADA guidelines

(2003) estimate that around 7% of pregnant women will be diagnosed with GDM and a previous narrative review of GDM prevalence in Europe estimated rates of between 2 and 6% (Buckley et al. 2012). The mean prevalence of GDM of 5.4% of pregnant women reported in the meta-analysis, although at the upper end of the estimates reported by Buckley et al. (2012), can be considered consistent with the Buckley et al. (2012) review given the differences in screening strategies used in included papers. A narrative review of GDM prevalence published at the same time as publication two, and including many of the same studies, reported median prevalence of 5.8% of pregnant women in Europe (Zhu and Zhang 2016).

There has been no consensus in previous research on the factors that influence GDM prevalence. As outlined in the discussion section of publication two, the findings of the meta-analysis regarding increasing prevalence with increasing maternal age and higher prevalence in Southern and Western Europe compared to Northern Europe are consistent with previous research (Buckley et al. 2012). Research conducted since the publication of paper two has similarly reported an association between maternal age and prevalence of GDM (Collier et al. 2017; Lavery et al. 2016). Publication two did not find any effect on prevalence for the well-established risk factors BMI, ethnicity or family history (Ben-Haroush et al. 2004). However, very few studies included in publication two reported on these factors, so it is likely that the meta-analysis had insufficient power to detect any effects of these risk factors on GDM prevalence.

The significant effect of diagnostic criteria on GDM prevalence reported in publication two was not consistent with the findings of the Buckley et al. (2012) narrative review. Buckley et al. (2012) reported that no consistent effect of diagnostic criteria on GDM prevalence was present. However, a study in Ireland that directly compared diagnostic criteria for GDM in one sample of women supported the findings of publication two (O'Sullivan et al. 2011). One of the strengths of meta-analysis is that it allows the effects of several variables to be assessed at the same time making it easier to identify patterns when there are relationships between variables. It may be that the narrative review by Buckley et al. (2012) was unable to identify an effect of diagnostic criteria on prevalence among the effects of other related variables.

As outlined in the discussion section of publication two, the significant increase found in prevalence over time is difficult to interpret because of increases in screening and changes

in diagnostic criteria in this time period. A retrospective study of over 3 million women with GDM in the US published after publication two reported temporal increases in GDM prevalence that were partly explained by BMI, race and maternal smoking but also clearly linked to changes in diagnostic criteria (Lavery et al. 2017) which supports the interpretation made in the discussion section of publication two.

By synthesising all the available research on this topic using meta-analysis, publication two provides clarity on some of the variations in the literature and offers a clear understanding of how many pregnant women have GDM and the demographic characteristics of these women. This publication is therefore useful not only as a reference paper for researchers writing about this topic, but also provides a basis for the planning of interventions and health care provision for the prevention of type 2 diabetes in women with GDM.

Publication four – progression from gestational diabetes mellitus to type 2 diabetes

Publication four was the first study in the UK to investigate progression from GDM to type 2 diabetes. The use of routinely collected health care data gives this study greater relevance to clinical practice and for informing the development of interventions based in health care settings. Publication four reported that around one quarter of women identified as having GDM in one health board in Scotland went on to develop type 2 diabetes over an average time period of eight years. This rate of progression to type 2 diabetes falls within the lower to middle end of the range of cumulative incidence figures reported in the Kim et al. (2002) systematic review of 2.6% to 70%. Kim et al. (2002) reported that incidence increased markedly in the first five years after delivery and plateaued after ten years which is broadly consistent with the average time period for progression to type 2 diabetes in publication four.

A comparison of the risk factors for progression to type 2 diabetes identified in publication four with findings of other research has been covered in depth in the discussion section of the published paper and this discussion will not be repeated here. To summarise, publication four found that weight during pregnancy, use of insulin during pregnancy, higher HbA1c levels at diagnosis of GDM, and FBG conferred the greatest risk of progressing from GDM to type 2 diabetes. Age, history of GDM in a previous pregnancy, and family history of diabetes were not found to be associated with an

increased risk of type 2 diabetes. Previous research was generally consistent with publication four regarding the findings for FPG and weight but were mixed for the other risk factors.

Since the publication of paper four a systematic review and meta-analysis has been carried out to quantify the risk of progression to type 2 diabetes in women who have had GDM (Rayanagoudar et al. 2016). This review included 39 studies (including publication four) with a total of 95,750 women with GDM. Consistent with publication four, this meta-analysis found an increased risk of developing type 2 diabetes in women with raised FPG, higher HbA1c, higher BMI and who used insulin during their pregnancy. In contrast to publication four, Rayanagoudar et al. (2016) found that advanced maternal age and family history of diabetes were risk factors for progressing to type 2 diabetes. However, hazard ratio estimates for these risk factors were raised in publication four and with a small sample size and wide confidence intervals it may be that the study lacked the power to detect effects for these variables.

The findings of publication four are largely supported by other research and suggest that women with higher FPG levels who use insulin during their pregnancy are at the highest risk of developing type 2 diabetes and should arguably be prioritised for preventative intervention. This study also suggests that there is a viable window of opportunity to prevent progression from GDM to type 2 diabetes in most women who are identified and treated during routine health care practice in Scotland.

Publication five – perceptions and experiences of women with gestational diabetes mellitus

There has been little research conducted in the UK exploring the perceptions and experiences of women with GDM and publication five is the first, to our knowledge, to be underpinned by health psychology theory. This basis in psychological theory has highlighted a range of illness perceptions and beliefs that may be impacting upon lifestyle change and could be addressed in a preventative intervention. Lifestyle interventions targeting people at risk of type 2 diabetes have not been as successful in women with GDM as they have in other high-risk groups (e.g. those with IGR; Gilinsky et al. 2015). This is likely because the challenges facing women with GDM in making lifestyle changes are potentially quite different to those facing other high-risk groups. Seeking the

views of women who have had GDM themselves is therefore important in helping to ensure that interventions are well received.

The findings of publication five are broadly consistent with those of a meta-synthesis of 16 qualitative studies assessing perceptions among women with GDM (Parsons et al. 2014) and with three further qualitative studies conducted in the UK and Ireland (Lie et al. 2013; McMillan et al. 2018; Tierney et al. 2015). With the exception of the McMillan et al. (2018) study, all of these studies were conducted before publication five. Themes summarised by these papers that are consistent with the present study include the emotional response to being diagnosed with GDM, loss of normal pregnancy, focus on the baby's health, perceived temporary nature of GDM, mixed understanding of causes of GDM, awareness of future risk of type 2 diabetes, lack of differentiation between different types of diabetes, lack of specific dietary advice, non-maintenance of lifestyle changes postnatally, barriers to postnatal lifestyle change and the acceptability of postnatal support for lifestyle change.

A finding of publication five that contradicted other research related to experiences of care during pregnancy. Studies included in the Parsons et al. (2014) review described women's negative experiences of the care received for GDM which is not generally consistent with publication five or the Lie et al. (2013) and McMillan et al. (2018) studies. These differences could be explained by the health-care contexts in which the studies were carried out. Publication five, the Lie et al. (2013) and the McMillan et al. (2018) studies were conducted in the UK whereas the studies included in the Parsons et al. (2014) review were conducted in regions outside of the UK including the United States, Sweden, Canada, Australia and Tonga. Participants in publication five, Lie et al. (2013) and McMillan et al. (2018) studies are therefore likely to have been receiving broadly comparable care based upon similar clinical guidelines during their pregnancy.

Although the transitory nature of GDM emphasised by some women in publication five was also reported in previous research (Parsons et al. 2014; Lie et al. 2013;), the belief that GDM is not an important, or even a real, diagnosis for some women is not one that has been reported in previous qualitative research. However, a survey of 100 women in the US found that 22% perceived that they had been misdiagnosed with GDM (Tang et al. 2016). This perception of misdiagnosis was more common among those who managed their GDM with diet alone. This supports the link made in publication five between the

lack of concern about GDM diagnosis and perception of GDM having a minimal impact on women's lives. In the Tang et al. (2016) study, the most common reasons given for perceiving a misdiagnosis included having blood sugar levels after diagnosis that were normal despite minimal changes in diet, borderline test results, concern about the new 2h 75g OGTT and the perception that women did not fit the typical profile of someone with gestational diabetes (not overweight and a healthy diet). With the exception of concern about the new diagnostic test, these are all reasons given by women in publication five who doubted their diagnosis.

The findings of publication five are generally consistent with the small body of other research on this topic in the UK and present some novel findings that add to our understanding of perceptions of misdiagnosis of GDM. The paper builds upon this research by using an explicit theoretical basis which helps to identify specific beliefs and perceptions that can be tackled by future interventions. Seeking women's views on preventative interventions also offers an idea of what type of intervention might be considered acceptable.

8.3 Intervention development

The publications in this thesis address several gaps in the literature which are important for the development of lifestyle interventions to prevent type 2 diabetes in people with IGR and GDM. This section of the chapter will firstly discuss the use of frameworks for intervention development. The implications of the findings of this thesis, and other research, for the development of interventions in people with IGR will then be considered using a framework for intervention development to structure the discussion. Finally, development of an intervention for women with GDM will be discussed, followed by a summary of recommendations arising from the thesis.

Frameworks for intervention development

Human behaviour is complex and influenced by a wide range of factors and consequently, interventions that aim to alter behaviour are often considered complex. Complex interventions are typically defined as those with several interacting components. The MRC (2006) identifies various additional dimensions that can also make an intervention complex, such as having a range of possible outcomes, having variability in the target population, allowing flexibility or tailoring of the intervention, targeting a number of

groups or organisations, and targeting multiple behaviours or difficult behaviours (MRC 2006). Preventative interventions for people with IGR and for women who have had GDM show a number of these aspects and can therefore be considered complex.

A number of frameworks have been proposed that aim to address some of this complexity including, among others, intervention mapping, PRECEDE-PROCEED model and the MRC framework for the design and evaluation of complex interventions (Bartholomew et al. 1998; Green and Kreuter 2005; MRC 2006). There is little evidence to suggest which of the many frameworks available is most appropriate for intervention development in the current context. The MRC guidance has been used in a variety of settings but is now over 10 years old with an updated version due to be published in 2019. A recent framework called 6SQuID (six steps for quality intervention development) published by Wight et al. (2016) will therefore be used to discuss development of interventions in the present context. This framework draws and builds on existing frameworks, including the MRC framework, and provides a six-step pragmatic guide to intervention development.

The six steps in the 6SQuID framework for intervention development are as follows:

1. Define and understand the problem and its causes.

2. Clarify which causal or contextual factors are malleable and have greatest scope for change.

3. Identify how to bring about change: the change mechanism.

4. Identify how to deliver the change mechanism.

5. Test and refine on small scale.

6. Collect sufficient evidence of effectiveness to justify rigorous evaluation/implementation

Each of these steps will be discussed in turn below with reference to the findings of this thesis and other research, first in relation to the development of an intervention for people with IGR and then for women with previous GDM.

Impaired glucose regulation intervention development

The first step of the 6SQuID framework requires researchers to define and understand the problem in question and its causes. Publications one and three in this thesis have helped to address the first step of this framework by clarifying the incidence and prevalence of IGR, and by identifying who is at most risk of progressing from IGR to type 2 diabetes, and therefore most likely to benefit from intervention. Publication one shows that around one in five people in the general population in Europe have IGR. In publication three 50,321 people with IGR were identified from routinely collected health care data over the five year study period. Although it was not possible to ascertain where diagnostic testing was conducted (i.e. primary or secondary care), these findings suggest that it may be feasible to deliver preventative intervention in health care settings without additional screening. Attempts to translate the success of randomised controlled trials of lifestyle interventions for prevention of type 2 diabetes to health care settings often face challenges including lack of resources, lack of practitioner time and practical difficulties with recruitment (Cardona-Morrell et al. 2010). Targeting interventions at those people who are already being identified by the health service as having IGR could help to overcome some of these challenges. The mean time for progressing from IGR to type 2 diabetes in publication three was 34 months suggesting that a timescale of up to three years after diagnosis would be appropriate for delivering an intervention in this group.

Once the nature and extent of the problem has been defined, the 6SQuID framework suggests that the influences or causes of the problem are explored (Wight et al. 2016). The review of literature presented in the introduction of this thesis identified the factors that cause IGR which include genetics, ethnicity and lifestyle (Nathan et al. 2007). The second step of 6SQuID is to clarify which of the causal or contextual factors are malleable and have greatest scope for change. Of the causal factors identified for IGR, lifestyle is the factor which has clear scope for change and as such is an appropriate target for intervention.

Publication three reported that of the people identified as having IGR, those with IGT, who were older, living in a more deprived area and male were at the greatest risk of progressing to type 2 diabetes. These findings suggest that these groups of people could arguably be targeted for lifestyle intervention. However, the evidence for IGT and sex as risk factors for progressing to type 2 diabetes is mixed suggesting further research is

needed before these groups are targeted. In publication three, people aged between 48 to 67 were at around a ten-fold risk of progressing to type 2 diabetes. As older age is a risk for type 2 diabetes in those without IGR, there is a clear rationale for focusing interventions on people in this age range.

The relationship between lower socioeconomic status and unhealthy lifestyle has been evidenced for a range of behaviours including physical activity and diet, two behaviours which are important in the prevention of type 2 diabetes in people with IGR (Pampel et al. 2010). Recent data from Scotland shows that the proportion of adults adhering to physical activity guidelines is highest in the least deprived areas and declines as deprivation increases (Scottish Government 2017a). Similarly, people living in the most deprived areas of Scotland have a poorer quality of diet (Whybrow et al. 2017) and are consistently more likely to be obese than those in affluent areas (Scottish Government 2017b). This socioeconomic gradient in health behaviour in Scotland may partly explain the increased risk of progressing to type 2 diabetes found in people from deprived areas with IGR in publication three. This evidence demonstrates that there is clear scope for an intervention to promote healthier lifestyles in people with IGR living in deprived areas.

The third step of the framework moves from understanding the problem in question to identifying how to bring about change. This involves developing a programme theory which defines the mechanism of change and describes how this mechanism will bring about changes in the targeted behaviour. The authors of the framework argue that the best developed programme theories are based upon theories of behaviour change (Wight et al 2016).

Once the change mechanism has been identified, the fourth step of the framework is to identify how to this change mechanism will be delivered. In this step an implementation plan is developed with the involvement of stakeholders where possible. At this point the researcher should also anticipate any potential unintended effects of the intervention and consider how to minimise these (Wight et al. 2016). If older people with IGR from deprived areas are to be targeted for intervention there are unique challenges to delivering interventions in this group that need to be considered.

Research on behaviour change interventions has frequently cited difficulties in recruiting and retaining people with low incomes (Carroll et al. 2011). Although there are

challenges in recruiting and retaining people with low incomes, a review of recruitment and retention in physical activity interventions reported strategies that have been successful with hard to reach groups, such as those with low incomes (Carroll et al. 2011). Successful recruitment strategies included using multiple advertising channels, partnering with respected community stakeholders and organisations, and having well-trained study staff who are culturally matched to the population of interest. Strategies for successful retention of participants included obtaining multiple contact numbers, making multiple contacts with participants, providing incentives, having a positive and caring attitude to participants, demonstrating sensitivity and respect for participants' situations, and being flexible regarding location and timing of study visits. Carroll et al. (2011) also highlighted the importance of using formative research to develop strategies for recruitment and retention in the specific context under study. Furthermore, the authors describe that successful studies typically made a significant effort to ensure interventions were appealing, tailored and as interactive as possible. The findings of this review suggest that with appropriate formative research and careful design, an intervention targeted at older people from deprived areas with IGR could be feasible.

In addition to recruitment and retention difficulties, there are also concerns about the effectiveness of behaviour change interventions for low income groups (Bull et al. 2014). A meta-analysis of interventions for healthy eating, physical activity and smoking in low income groups published between 2006 and 2014 reported only small positive effects on these three behaviours. However, similar reviews of studies that did not target low income groups tended to report larger effect sizes (Bull et al. 2014). Although it is not possible to make a true comparison without studies that compare the same intervention between a group with low income and a group including people with higher incomes, these findings do suggest that behaviour change interventions may be less effective for low-income groups.

Analysis of the variance within the physical activity studies included in the Bull et al. (2014) meta-analysis showed that there were larger effect sizes in studies that targeted only physical activity compared to those targeting multiple behaviours (Bull et al. 2014). Another meta-analysis on the same topic covering literature published between 1995 and 2006 also reported that interventions with fewer behaviour change techniques tended to be more effective, although this finding was only marginally significant (Michie et al.

2009). These findings suggest that an intervention for people with IGR from deprived areas may be most effective if it targets only one behaviour and contains a small number of behaviour change techniques.

The remaining two steps of 6SQuID are to test and refine the intervention on a small scale and to collect sufficient evidence of effectiveness to justify rigorous evaluation/implementation. The authors of the 6SQuID framework stress that intervention development is not a linear process and researchers will often return to earlier stages before reaching the final stage of development (Wight et al. 2016). Using a framework allows a systematic approach to be taken to intervention development and evaluation and allows effective components of the intervention to be identified. This is important for maximising the effectiveness of interventions and ensuring resources are not wasted (Wight et al. 2016). The findings of this thesis contribute to understanding of the early stages of this framework allowing future research to build on this and address these later stages of development.

Gestational diabetes mellitus intervention development

Publications two and four in this thesis have helped to address the first step of the 6SQuID framework for intervention development, which is to define and understand the problem and its causes, by clarifying the prevalence of GDM and identifying who is at most risk of progressing from GDM to type 2 diabetes, and therefore most likely to benefit from intervention (Wight et al. 2016). Publication two shows that 5.4% of the general population of pregnant women developed GDM in Europe. The findings of this publication give a clear understanding of the prevalence of GDM on which to base the planning of an intervention. Publication four found that one quarter of women with GDM in one area of Scotland developed type 2 diabetes after a mean time period of eight years. This study, alongside the systematic review by Kim et al. (2002) which found that incidence of type 2 diabetes was most rapid in the first five years after GDM and plateaued after ten years, suggests that an intervention for women who have had GDM should ideally be provided within five years after women deliver to allow time for lifestyle changes to be made.

Publication four reported that increased weight during pregnancy, use of insulin during pregnancy, higher HbA1c levels at diagnosis of GDM and fasting blood glucose were all

associated with an increased risk of developing type 2 diabetes after GDM. Of these factors, increased weight and FPG were most consistently supported by previous literature suggesting that women with these risk factors should be targeted for intervention. However, the practicalities of targeting women with these risk factors would need to be considered as the effort needed to identify these women may not prove to be time or cost effective. This is something that would need to be explored with stakeholders during the later stages of intervention development described below.

The second stage of the 6SQuID framework is to clarify which causal factors are malleable and have greatest scope for change (Wight et al. 2016). Causal factors for GDM include increased maternal age, obesity, ethnicity and family history of diabetes (Bellamy et al. 2009). Of these factors, diet and physical activity behaviours associated with obesity are the causal factors that have the clearest scope for change and are therefore an appropriate target for intervention. A review of research examining health behaviours in women with previous GDM found that they are less likely to meet physical activity recommendations and less likely to have adequate intake of fruit and vegetables (Jones et al. 2009). The finding of the Jones et al. (2009) study and the difficulties reported by women in publication five in maintaining a healthy diet and physical activity levels suggest that there is scope to improve both physical activity levels and dietary behaviour in women with previous GDM.

Women interviewed for publication five were generally open to receiving an intervention to address either diet or physical activity, but some women expressed a preference for support for changing one of these behaviours over the other. A review of postpartum lifestyle interventions to prevent type 2 diabetes in women with previous GDM found that effective interventions typically included changes to diet and physical activity (Guo et al. 2016). These findings suggest that an intervention for women with previous GDM should target both diet and physical activity but with the option to tailor the intervention to address a single behaviour according to individual preference.

The third stage of intervention development, according to the 6SQuID framework, is to identify how to bring about change. The authors of the framework argue that the best developed interventions are based on theories of behaviour change (Wight et al. 2016). The semi-structured interviews conducted in publication five were informed by psychological theory and are therefore particularly helpful for identifying the potential

mechanism of change in an intervention for women with previous GDM. The interviews identified several illness perceptions that could be addressed by an intervention, in particular those relating to identity and consequences of GDM and timeline and consequences of type 2 diabetes. Specifically, many women did not see GDM as an important, or in some cases a real diagnosis, because of the minimal impact that it had on their lives. Similarly, women were unconcerned about their future risk of type 2 diabetes. In some women the lack of follow up care reinforced their perception that GDM and type 2 diabetes were not serious conditions.

According to Leventhal's SRM of illness (1992), women with GDM will interpret information about their diagnosis to build up an understanding of the condition formed around various illness perceptions (identity, cause, timeline, consequences, control/cure and coherence). The model proposes that the way women respond to their illness is influenced by both these perceptions and by their emotional response to the illness (Leventhal et al. 1992). Consistent with this model, women in the present study reported that they were motivated to make changes to their diet by concern for their baby's health, but most did not maintain these changes after giving birth as they viewed their GDM as being resolved. By addressing identity and consequences of GDM and timeline and consequences of type 2 diabetes in an intervention, the aim is that women will view lifestyle change as an appropriate and successful coping strategy for preventing future type 2 diabetes. Furthermore, it is hoped that receiving additional aftercare in the form of a preventative intervention will indirectly alter perceptions about the seriousness of GDM and type 2 diabetes.

Other findings in publication five that are important for intervention development are those regarding the barriers to lifestyle change in the postnatal period. Tiredness, lack of energy and the demands of looking after a new baby were highlighted as barriers to lifestyle change by women interviewed in publication five. The TPB proposes that someone's perceived ability to perform a given behaviour (perceived behavioural control), such as physical activity or dietary changes, has both a direct influence on the behaviour and an indirect influence via intention (Ajzen 1992). The TPB predicts that even if women intend to maintain lifestyle changes after giving birth, a belief that they are not able to because of barriers such as lack of energy may prevent them from being successful. Addressing perceived behavioural control is particularly important in an

intervention for women with previous GDM as some women reported feeling concerned or fearful about their diagnosis of GDM or their future risk of type 2 diabetes. Research has shown that fear of a disease without a concurrent message to encourage the individual's confidence in their ability to prevent the disease can result in lower motivation and defensive coping responses such as avoidance (Witte and Allen 2000).

The findings of publication five show that although there were some commonalities in the perceptions and beliefs held by women with previous GDM, the variations found from individual to individual suggest that an intervention would need to be tailored according to the women's specific beliefs and perceptions. In particular, it may be valuable to assess illness perceptions in relation to GDM and type 2 diabetes and perceived behavioural control for postnatal lifestyle change and tailor the intervention according to the specific beliefs and perceptions held by individual women.

After identifying the mechanism of change, the next step in the 6SQuID framework is to identify how to deliver the change mechanism. The demands on women in the postpartum period reported in publication five and other research (Lie et al 2013; McMillan et al. 2018), and issues with recruitment to previous postnatal preventative interventions in women with GDM (Gilinsky et al. 2015), highlight the importance of careful consideration of the optimal timing and method of delivery for an intervention in this group. It has been suggested that the optimum time for starting a preventative lifestyle intervention is soon after the diagnosis of GDM during pregnancy (Ferrara et al. 2011). Ferrara et al. (2011) argue that a diagnosis of GDM is a teachable moment and that an intervention started soon after this diagnosis can take advantage of the motivation women have to make lifestyle changes driven by concern for their baby's health. However, the findings of publication five and other research in the UK show that women in the UK are largely satisfied with the support they receive after a diagnosis of GDM to help them make the necessary lifestyle changes, and that the motivation to make lifestyle changes in response to a diagnosis of GDM was not sufficient for change to be maintained postnatally (Lie et al 2013). Women in these studies did however highlight a lack of care and a sense of abandonment in the postnatal period, suggesting that in the UK context an intervention delivered in the postnatal period may be most appropriate.

The findings of publication five and other qualitative research (Lie et al. 2013; Parsons et al. 2014) suggest that the early postnatal period may be too soon for a preventative

intervention because of the demands of looking after a new-born baby and recovery from childbirth. The study by Lie et al. (2013) suggested that women may be receptive to an intervention when their baby is around six months old and they have starting weaning as women report feeling conscious of their own and their baby's eating habits at this time. Although this research points to the latter half of the first year postnatally as being an appropriate time to deliver an intervention, the acceptability of this timing would need to be explored as part of the assessment of the feasibility of an intervention.

In addition to the timing of an intervention for women with previous GDM, the mode of delivery also needs to be considered. An intervention for this group of women needs to be delivered in a way that takes account of their family and work commitments. One possible approach to intervention delivery that might help to minimise some of these barriers would be to deliver an intervention during women's existing health care appointments complemented with mobile health technology.

Clinical guidance in Scotland and England recommends that women with GDM are tested for diabetes approximately six weeks postpartum and annually thereafter (SIGN 2014; NICE 2008). These appointments could offer an opportunity for delivering a preventative intervention to women with GDM. However, a retrospective study of 127 primary care practices in England found that postpartum testing was only performed in 18.5% of women within six months of delivery and annual rates of postpartum testing were only around 20% (McGovern et al. 2014). While there are no studies assessing uptake of postnatal testing for diabetes in Scotland, findings from the interviews conducted for publication five (findings related to postnatal testing were not discussed in the publication) suggest that postnatal testing in Scotland is also far from universal. These findings suggest that at present alternative opportunities to deliver preventative interventions need to be explored. I am involved in a study due to commence in 2019 that will assess the feasibility of delivering preventative interventions to women with previous GDM during health visitor appointments or cervical screening appointments (Evans et al. 2018).

Mobile technology is an avenue for intervention delivery in health that is receiving increased attention with the worldwide spread of mobile technologies. Mobile health technology is defined by WHO as medical or public health practices supported by mobile devices such as mobile phones or other wireless devices (WHO 2011b). Mobile devices

have a range of functions that may be utilised in health interventions, including text and media messages, telephone, web access, multimedia playback, social media and other applications (Free et al. 2013). Mobile health interventions have been applied to health behaviour change (e.g. smoking cessation) and to improve disease management (e.g. management of diabetes; Free et al. 2013).

Advantages of mobile health technology interventions is that they are typically low cost, can be tailored to individual patients and can be used to relay data directly to the researcher. The flexibility and convenience that mobile health technology offers may mean that this approach would be well suited to women with young babies (McMillan et al. 2016). There is some evidence to support the effectiveness of mobile technology in health behaviour change interventions (Afshin et al. 2016) and findings from semi-structured interviews with 27 women recruited from one hospital in England suggest that women feel there is a role for technology in supporting lifestyle change postnatally. These findings together suggest that an intervention combining existing health appointments and mobile technology may be a suitable approach for a lifestyle intervention for women with previous GDM.

As discussed in the section on intervention development for people with IGR, the final steps of the 6SQuID framework are to test and refine the intervention on a small scale and collect sufficient evidence of effectiveness to justify rigorous evaluation/implementation (Wight et al. 2016). The findings of this thesis contribute to understanding of the early stages of this framework and provide a basis for further research to explore the latter stages of the framework. The findings of the thesis provide clear suggestions for the content, timing and mode of delivery for interventions to prevent type 2 diabetes in women with previous GDM. Further research is needed to explore the feasibility and acceptability of these suggested avenues for intervention.

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Appendices

Appendix 1

Statement of author contributions to publications.

Publication 1:

Claire Eades was primarily responsible for the study design, screening, data extraction, analysis and drafted the manuscript. Josie Evans and Emma France assisted in the design, screening, analysis and drafting the manuscript.

Publication 2:

Claire Eades designed the study, assisted with screening of data, conducted data extraction, performed analyses and drafted the manuscript. Josie Evans assisted with screening papers, analyses and drafting the manuscript. Dawn Cameron assisted with screening papers, analyses and drafting the manuscript.

Publication 3:

Claire Eades was primarily responsible for gaining access to the data, analysis and drafting the manuscript. Both Graham Leese and Josie Evans assisted in the analysis and drafting of the manuscript.

Publication 4:

Claire Eades was primarily responsible for gaining access to the data, data extraction, analysis and drafting the manuscript. Graham Leese was involved in conceiving the study, acquisition of data and drafting of the manuscript. Maggie Styles carried out data extraction and drafting of the manuscript. Josie Evans was involved in conceiving the study, data analysis and drafting the manuscript. Helen Cheyne participated in drafting and revising the manuscript.

Publication 5:

Claire Eades conducted the fieldwork and was primarily responsible for designing the study, analysis of the data and drafting the manuscript. Josie Evans and Emma France assisted with analysis of the data and drafting and revising the manuscript.

Appendix 2

Supplementary file for publication 1 containing table 2.

Table 2: Characteristics of included studies.

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
IGT											
Andersson Sweden 2002-2005	Stratified random sample of two areas drawn from census (Vara and Skövde; population approx. 66,000).	2502	Men: 46.8 Women : 46.5	30-75	48	WHO 1999 (3)	NR	7.1% (5.6-8.5)	9.6% (8-11.2)	NR	1
Brohall Sweden 2001-2004	Whole population of women aged 64 in one region drawn from county register (Gothenburg; population 4856).	2595	N/A	64 only	0	WHO 1999 (3)	N/A	N/A	22% (20.4-23.6)	N/A	2
Castell Spain 1994-1995	Stratified random sample of 41 towns drawn from census	2214	NR	30-89	44.1	WHO 1985 (2)	Age and sex standardised 11.6%	Age standardised 11.2% (9.2 – 13.2)	Age standardised 12% (10.2-13.8)	Significant increase with age in men	2

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
	(population 3,495,434)						(10.3-12.9)			and women	
Chatuverdi UK NR (published 1994)	Stratified random sample of patients from six GP surgeries in one area of a city drawn from GP lists (Brent, London)	1166	NR	46-64	46.7	WHO 1985 (52 or 4?)	9.1% (6.8-11.4)	9.1% (5.8-12.6)	9.0% (5.8-12.2)	NR	2
Cruickshank UK NR (published 1991)	Stratified random sample of two practices in one area of a city (North-West London) drawn from family practitioner committee population registries	101	Men: 62 (7) Women : 60.3 (7)	45-74	48.5	WHO 1985 (2 or 4?)	18.8% (11.2-26.4)	Age adjusted prevalence: 25% (12-37)	Age adjusted prevalence: 14% (4-23)	NR	1

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
Garancini Italy 1990	Random sample of three areas (Cremona, Casalbuttano and Vescovato; population 38634) drawn from those registered on regional list.	1797	NR	45+	43	WHO 1980 (1)	8.4% (7.1-9.7)	7.7% (5.7-9.7)	8.9% (7-10.8)	Significant increase with age in men and women	2
Hiltunen Finland 1992	Whole population aged 70 to 93 years in three areas (Kempele, Oulunsalo and Hailuoto; population 501) drawn from official population registries (residents legally required to register).	379	Men: 75.7 (4.9) Women: 76.8 (5)	70-93	37	WHO 1985 (2)	34% (29.3-38.8)	31.9% (24.2-39.6)	35.3% (29.2-41.4)	NR	1
Larsson Sweden	Whole population of women aged 55-57 in one area (Malmö; population 2745).	1843	NR	55-57	0	WHO 1985 (2)	N/A	N/A	27.9% (25.9-30.0)	NR	3

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
1986-1987 and 1990-1991	Doesn't report where names drawn from.										
Mykkänen Finland 1986-1988	Random sample of one area (Kuopio) drawn from population registry.	1300	Men: 68.9 Women : 69.1	65-74	36.2	WHO 1985 (4)	18.6 (16.5-20.7)	17.8% (14.4—21.3)	19.1% (16.4-21.7)	NR	1
Rajala Finland 1992	Whole population aged 55 in one area (Oulu; population 1008). Doesn't report where names drawn from.	717	N/A	55 only	43	WHO 1985 (2)	27% (24.2-30.7)	28.6% (23.5-33.6)	26.7% (22.4-30.9)	NR	3
Tuomileho Finland 1984	Whole population of men aged 65-84 in two areas. Doesn't report where names drawn from.	763	72.6	65-84	100	WHO 1995 (2)	N/A	31.8% (28.4-35.3)	N/A	No significant increase found with age.	3

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
Unwin UK 1993-1994	Systematic stratified sample in one region (Newcastle; population 6448) drawn from Newcastle family health services authority patient register.	610	NR	25-64	49.6	WHO 1985 (2)	10.1 (7.7-12.4) 12.8 (10.1-15.4)	12.5% (8.8-16.2)	Age adjusted 9.7% (6.4-13.0)13.1% (9.3-16.8)	NR	2
Verrillo Italy 1981-1982	Whole population aged over 18 in one area (Sanza; population 1362) drawn from registry office data.	1154	NR	18-92	45.8	WHO 1980 (1)	6.4% (5-7.8)	4.9% (3.1-6.8)	7.7% (5.6-9.8) Age adjusted: 7.9%	Significant increase with age in men and women.	1
IFG											

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
Almoosawi UK 2008	Random cluster sample from the whole of UK drawn from postcode address file. Those who completed 3 or 4 days of a diet diary were eligible to give a blood sample.	633	NR	19+	41	Fasting 6.1-6.9mmol/l (2)	8.7 (6.5-10.9)	10.5% (6.7-14.2)	7.5% (4.8-10.1)	Significant increase in age for women but not men.	3
Baena-Díez, Spain 1995 and 2000	Stratified random sample of 33 towns in one area (Girona; population 303,903) drawn from census.	4801	NR	25-74	48.5	Fasting 6.1-6.9 mmol/l (2)	10%	NR	NR	NR	1
Bernal-Lopez Spain 2007	Random sample of one health centre in Malaga (population 29,818) drawn from health centre list.	2144	42 (15.2)	18-80	49.9	ADA 2003 (1)	16.3% (14.7-17.8)	NR	NR	NR	2

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
Bonaldi France 2006-2007	Stratified random sample of whole country drawn from phone lists.	2012	NR	18-74	37	WHO 1999 and ADA 2003 (1+2)	WHO 1999: 5.6% (4.3-7.4) ADA 2003: 15.5% (13.2-18.1)	WHO 1999: 7.9% (5.7-10.9) ADA 2003: 19.9% (16-24.5)	WHO 1999: 3.4% (2.3-5.1) ADA 2003: 11.2% (8.9-13.8)	No significant increase.	3
Bourdel-Marchasson France 1999-2001	Whole population aged 65 and over in three areas (Bordeaux, Dijon, Montpellier; population 1,134,321) drawn from electoral register.	8564	74.2 (5.5)	65+	39.3	WHO 1999 (2)	3.6% (3.3-4.1)	4.2% (3.6-4.9)	2.8% (2.4-3.3).	NR	3
Gasull Spain	Random sample of one area (Catalonia; population	886	45.1 (15)	18-74	42.9	WHO 2006 (2)	23% (20.0-25.6)	Subjects with IFG significantly more		NR	3

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
2002	6,506,440) drawn from census.							likely to be male than those without IFG.			
Gourdy France 1995-1997	Stratified random sample of three areas (Lille, Bas-Rhin, Haute-Garonne) drawn from electoral register.	3248	NR	35-64	50.9	ADA 1997 (2)	Age adjusted: 8.5% (7.6-9.4)	12.3% (10.7-13.8)	5.6% (4.5-6.7)	Significant increase with age in men and women	2
Muntoni Italy 2002-2005	Stratified random sample of four areas (Ploaghe, Sorso, Sinnai, Maracalagonis; population 39,624) drawn from municipal records.	4737	NR	20+	47	WHO 1999 (2)	10.3% (9.4-11.2)	12.2% (12.1-12.4)	9.9% (9.7-10.1)	NR	1
Panagiotakos Greece	Random sample of one area (Attica).	3042	NR	18-89	49.7	ADA 2006 (1)	16.2% (14.9-17.5)	20.5% (18.4-22.5)	12% (10.4-13.7)	NR	3

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
2001-2002	Doesn't report where names drawn from.										
Thomas UK 1999-2001	Random sample of patients from 24 general practices across Britain drawn from general practice lists.	7378	NR	60-79	50.6	WHO 1999 (2)	17.7 (16.9-18.6)	17.9% (16.6-19.1)	17.6% (16.4-18.9)	NR	2
Valverde Spain 2006	Stratified random sample of patients in the 12 health care centres in one region (Murcia; population 901,920) drawn from health care centre lists.	1570	47.4 (17.7)	20+	NR	ADA 1997 (2)	4.9% (3.9-6.1)	6.3% (4.6-8.3)	3.7% (2.5-5.2)	Significant increases with age in both men and women	2
IGT and IFG											

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
Bennet Sweden 2010	Random sample of one area (Rosengård; approx. population 22,000) drawn from census.	79	NR	45-65	56	WHO 1999 for IGT (3) and IFG (3)	IGT: 10.1% (3.5-16.8) IFG: 15.2% (7.3-23.1)	NR	NR	NR	3
Bonora Italy 1990	Random sample of one area (Bruneck; population 4793). Doesn't report where names drawn from.	919	NR	40-79	50.6	WHO 1999 for IGT (3) and IFG (3)	IGT: 5.7% (4.3-7.3) IFG: 5.9% (4.5-7.5) IGT+IFG: 2.1% (1.1-3.0)	NR	NR	NR	3
Boronat Canary	Stratified random sample of one area (Telde; population	1030	48 (11.9)	30-82	43.5	WHO 1999 (IGT not clear if 2 or 4; IFG not	IGT: 10.4%	Age adjusted	Age adjusted	NR	1

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
Islands, Spain NR (published 1998)	42, 451) drawn from census.					clear if 1 or 3)	(8.5-12.3 IFG: 3.1% (2-4.2)	IGT:11.4% (8.4-14.3) IFG: 3.3% (1.7-5.0)	IGT: 9.6% (7.2-12.0 IFG: 2.9% (1.6-4.3		
Cederberg Finland Baseline: 1996-1998 10 year follow up: 2007-2008	Whole population aged 61 to 63 in one area (Oulu; population 831). Doesn't report where names drawn from.	Baseline:499 10 year follow up: 384	NR	61-63	40.3	WHO 1999 for IGT (3) and IFG (3)	Baseline IGT: 18.7% (15.2-22.1) IFG: 7.2% (4.9-9.5) IGT+IFG: 2.7% (1.2-4.0) Follow-up	Follow up IGT: 20.8% (14.7-27.0) IFG: 16.1% (12.5-19.8)	Follow up IGT: 19.4% (14.6-24.2) IFG: 7% (4.5-9.6)	NR	3

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
							IGT: 20% (16.2-23.7) IFG: 10.6% (7.6-13.5)				
de Pablos-Velasco Canary Islands, Spain NR (published 2001)	Stratified random sample of one town (Guia; population 6355) drawn from municipal list.	691	NR	30+	NR	WHO 1985 for IGT (2) and ADA 1997 for IFG (2)	IGT: 17.1% (14.3-19.9) IFG: 8.8% (6.7-10.9)	IGT: 16.1% (11.9-20.2) IFG: 10.8% (7.3-14.3)	IGT: 17.9% (14.1-21.7) IFG: 7.3% (4.7-9.8)	No significant increases in IFG with age for men or women. Significant increase in IGT for men only between those	1

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
										aged 30-39 (6.1%; -0.6-12.8) and those aged 80+ (19%; 2.3-35.8)	
de Vegt plus Heine and Mooy Netherlands 1989-1992	Random sample of one town (Hoorn, population 57,000) drawn from population register.	2378	Men: 61.2 (7.3) Women: 61.8 (7.4)	50-74	46	WHO 1985 for IGT (4) and ADA 1997 for IFG (2)	IGT: 10.3% (9.1-11.5) IFG: 12% (10.7-13.3)	IGT: 9.2 (7.5-10.9)	IGT: 11.2 (9.6-12.8)	IGT appears to increase with age for men and women but no CIs or significance testing.	1
Gardete-Correia Portugal 2009	Random sample of 122 areas drawn from census.	5167	NR	20-79	NR	WHO 1999 for IGT (3) and IFG (3)	IGT: 12.6% (11.6-13.6%) IFG: 8.2%	IGT: 12.1 (10.7-13.5) IFG: 11.8 (10.4-13.2)	IGT: 13.2 (12.0-14.4) IFG: 6.0 (5.2-6.8)	Significant increases with age for IGT,	1

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
							(7.4-9.0%) IGT + IFG: 2.4% (1.9-2.9)	IGT+IFG: 2.9 (2.2-3.6)	IGT+IFG: 2.1 (1.6-2.6)	IFG and IGT+IFG.	
Glümer plus Borch-Johnsen Denmark 1999-2001	Stratified random sample of one area of a city (Copenhagen; population 13,016) drawn from civil registration system.	6784	46 (7.9)	30-60	48.7	WHO 1999 for IGT (3) and WHO 1999 and ADA 2003 (1+3)	WHO 1999 IGT: 12% (11.2-12.8) IFG: 11.8% (11.0-12.6) ADA 2003 IFG: 37.6%	IGT: 30-35 years 9.9% IFG significantly higher in men	IGT: 30-35 years 5.8%	NR	2

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
							(36.4-38.8)				
Harris UK 1994-1996	Random sample of patients in 9 general practices in area of a city (Wandsworth, London) drawn from general practice lists.	380	49.8	40-59	NR	WHO 1999 for IGT (3). ADA 1997 and WHO 1999 for IFG (2+3)	WHO 1999 IGT: 7.9% (5.2-10.6) IFG: 1.6% (0.3-2.8) ADA 1997 IFG: 2.9% (1.2-4.6)	NR	NR	NR	2
Lilja plus Eliasson Sweden	Stratified random sample of two areas drawn (Norbotten and Vaserbotten)	2830	NR	25-64	48	WHO 2006 for IGT (2) and IFG (2)	1990 IGT 5.8% (4.2-7.4)	1990 IGT: 3.5% (1.1-6.0);	1990 IGT: 7.8% (5.0-10.7)	NR	1

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
1990, 1994, 2004 and 2009	from population registry.						IFG 7.2% (5.4-9) 1994 IGT 7.5% (5.6-9.3) IFG 5.6% (4-7.3) 2004 IGT 7.5% (5.6-9.5) IFG 12.1% (9.7-14.5) 2009 IGT 12.4%	IFG: 10.1% (7.0-13.2) 1994 IGT: 6.7% (4.3-9.2) IFG: 9.3% (6.2-12.4) 2004 IGT: 5.4% (2.9-7.9) IFG: 10.6% (7.6-13.6) 2009 IGT: 10.1% (7.2-12.9) IFG: 12.6% (9.1-16.2)	IFG: 4.5% (2.2-6.7) 1994 IGT: 8.2%(5.3-11.1) IFG: 2.0% (0-4.4) 2004 IGT: 9.7% (6.6-12.8) IFG: 10.5% (8.2-12.8) 2009 IGT: 14.5% (11.2-17.9) IFG: 7.7% (5.0-10.4)		

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
							(9.7-15.1) IFG 10.3% (7.8-12.8)				
López Spain 2004	Random cluster sample of one area (Galicia) drawn from public health service database.	2848	41.4 (15)	18-85	46.4	ADA 2002 for IGT (3) and IFG (3)	IGT: 4% (3.3-4.7) IFG: 12.9% (11.7-14.1) IGT+IFG: 4% (3.3-4.7)	NR	NR	NR	3
Meisinger Germany 2006-2008	Stratified random sample of one region (Augsburg; approx. population 600,000) drawn from population registries.	1653	NR	35-59	54.2	WHO 1999 for IGT (3) and IFG (3)	IGT: 6.3% (5.1-7.4) IFG: 2.9% (2.1-3.7)	IGT: 6.4% (4.7-8.1). IFG: 4.2% (2.8-5.7)	IGT: 6.3% (4.7-7.8) IFG: 1.9% (1.1-2.8)	IFG, IGT and IGT+IFG increased with age.	2

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
							IGT+IFG: 1.1% (0.6-1.5).	IGT+IFG: 1.7% (0.8-2.6)	IGT+IFG: 0.6% (0.1-1.0)		
Qiao plus Tuomilehto Finland 1987	Stratified random sample of three areas (North Karelia, Kuopio, Turku-Loimaa) drawn from population register.	2718	NR	45-64	46.9	WHO 1985 and 1999 for IGT (2+3) and WHO 1999 for IFG (3)	WHO 1985 IGT: 4.3% (3.6-5.1) WHO 1999 IGT: 12.4% (11.2-13.6) IFG: 4% (3.3-4.7) IGT+IFG: 1.5% (1.1-2.0)	WHO 1985 IGT 3% (2.0-3.9)	WHO 1985 IGT 5.5% (4.4-6.7)	IGT appears to increase with age but no CIs or significance testing.	2

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
Rathmann Germany 1999-2001	Stratified random sample of one region (Augsburg; approx. population 600,000) drawn from population registries.	1353	NR	55-74	NR	WHO 1999 for IGT (3) and IFG (3)	IGT: 16.4% (13.8-18.2) IFG: 7% (5.9-8.1)	IGT: 16.8% (14.1-19.4) IFG: 9.8% (7.6-11.8)	IGT: 16% (13.3-18.6) IFG: 4.5% (3.0-6.0)	Group 1 IGT increased with age in both sexes ($p<0.001$). IFG increase with age in women only ($p<0.05$).	2
Saaristo Plus Wikström Finland 2004-2005	Stratified random sample of three areas (Pikanmaa, South Ostrobothnia and Central Finland) drawn from population register.	2824	59.8 (8.5)	45-74	48.2 %	WHO 1999 for IGT (3) and IFG (3)	IGT: 16.2% (14.9-17.6) IFG: 7.5(6.5-8.5)	IGT: 15.5% (13.5-17.6) IFG: 10% (8.2-11.8).	IGT: 17% (15-19.1). IFG: 5.2% (3.9-6.5).	IGT significantly increased in men and women with age. IFG significan	2

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
										tly increased with age in men but not women.	
Soriguer, Goday Spain 2009-2010	Random cluster sample of whole country. Doesn't report where names drawn from.	3090	NR	18+	41.6	WHO 1999 for IGT (3) and IFG (3)	IGT: 9.2% (8.2 – 10.2) IFG: 3.4% (2.9-4.0) IGT+IFG: 2.2% (1.7-2.7)	Prevalence of IGR significantly greater in men.		Prevalence of IGR significantly increases with age.	3
Soriguer, Rojo-Martínez Spain 1997-1998	Random sample of one town (Pizarra; population 6,600) drawn from census.	910	38.9 (13)	18-65	NR	WHO 1999 for IGT (3) and IFG (3)	IGT: 9.7% (7.8-11.6) IFG: 14.2%	NR	NR	NR	1

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
							(11.9-16.4) IGT+IFG: 4.5% (3.2-5.9)				
Valdés Spain 1998-1999	Random sample of people from in one area (Asturia). Doesn't report where names drawn from.	1034	NR	30-75	NR	WHO 1999 for IGT (3) and IFG (3)	IGT: 8.9% (7.2-10.6) IFG: 4.1% (2.9-5.3) IGT+IFG: 3.5% (2.4-4.6).	NR	NR	NR	3
Webb UK 2005-2008	Random sample of patients from 20 general practices in one city (Leicester; population 149,311)	4688	54.3 (10.5)	40-75	50.2	WHO 1999 for IGT (3) and IFG (3)	IGT: 9.1% (8.2-9.9)	NR	NR	NR	3

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
	drawn from general practice list.						IFG: 2.7% (2.2-3.1) IGT+IFG: 1.7% (1.4-2.1)				
Wild UK 1988-1989	Stratified random sample of patients from 11 general practices in one city (Edinburgh) drawn from general practice lists.	1592	NR	55-74	51	WHO 1999 for IGT (3) and IFG (3)	IGT: 8.1% (6.8-9.4) IFG: 11.6% (10.0-13.2) IGT+IFG: 3.2% (2.3-4.1)	IGT: 10.5% (8.3-12.6) IFG: 14% (11.6-16.5) IGT+IFG: 4.2% (2.8-5.6)	IGT: 5.6% (3.9-7.2) IFG: 8.5% (6.5-10.5) IGT+IFG: 2.4% (1.3-3.5).	NR	2
Williams plus Forouhi	Random sample of people aged 40-64 in one general practice in the city of Ely	1122	NR	40-64	43	WHO 1985 for IGT (unclear if 2 or 4).	IGT: 16.7%	IGT: 14.7 (11.6-17.8) ADA 1997	IGT: 17.4 (14.5-20.3)	NR	1

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
UK 1990-1992	(approx. population 4922).					ADA 1997 and ADA 2003 for IFG (1+2)	(14.5-18.8) ADA 1997 IFG: 24.7% (22.1-27.3) ADA 2003 IFG: 36.1% (33.1-39)	IFG: 32.5% (28.2-36.9) ADA 2003 IFG: 39.2% (34.5-43.5)	ADA 1997 IFG: 18.9% (15.7-22.0) ADA 2003 IFG: 33.8% (30.0-37.6)		

First Author, Country, Years data collected	Sampling Method	Sample Size	Mean Age (SD)	Age Range	% Male	Criteria Used (category)	Prevalence (95% CI) Overall	Male	Female	By age	Quality Score (1 higher to 3 lower quality)
Ylihärsilä Finland 1992	Stratified sample from three areas (North Karelia, Kuopio, Turku-Loimaa) drawn from the population register	2087	NR	45-64	45.8	WHO 1999 for IGT (3). WHO 1999 and ADA 1997 for IFG (3+2)	WHO 1999 IGT 10% (8.7-11.3) IFG 8.8% (7.6-10.0) ADA 1997 IFG 13% (11.6-14.5)	WHO 1999 IGT 10.8% (8.8-12.7) IFG 13.4% (11.2-15.5) ADA 1997 IFG 18.6% (16.2-21.1)	WHO 1999 IGT 9.4% (7.7-11.1) IFG 4.9% (3.6-6.1) ADA 1997 IFG 8.3% (6.7-9.9)	IGT significantly increased with age No significant increase in IFG with age.	1

Appendix 3

PDF of published manuscript for publication 1.

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Prevalence of impaired glucose regulation in Europe: a meta-analysis

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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 with 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.

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] whereas 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 2 h plasma glucose (2hPG) concentration after an oral glucose tolerance test of between 7.8 and 11.1 mmol/l

and a fasting plasma glucose (FPG) concentration of <7 mmol/l. The ADA define IFG as an FPG of between 5.6 and 6.9 mmol/l and WHO define it as an FPG of between 6.1 and 6.9 mmol/l and (if measured) a 2hPG in the normal range (<7.8 mmol/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.[3] 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 nine 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 (IGT or IFG or prediabetes or pre-diabetes or IGR). 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 (C.E.E., E.F.F and I.M.M.E.) 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 C.E.E., E.F.F and I.M.M.E. as 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 IGR 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 (C.E.) 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: (i) 2hPG 7.8–<11.1 mmol/l (e.g. ADA 1997)[3]; (ii) FPG <8.0 mmol/l and 2hPG 8.0–<11.0 mmol/l (e.g. WHO 1980)[12]; (iii) FPG < 7.8 mmol/l and 2 h 7.8–<11.1 mmol/l (WHO 1985)[13] and (iv) FPG <7.0 mmol/l and 2hPG 7.8–<11.1 mmol/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: (i) FPG 5.6–6.9 mmol/l (e.g. ADA 2003)[14]; (ii) FPG 6.1–6.9 mmol/l (e.g. ADA 1997)[3]; (iii) FPG 6.1–6.9 and 2hPG <7.8 mmol/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 h 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 (C.E.) 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 5594 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 Supplementary table S1 (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.

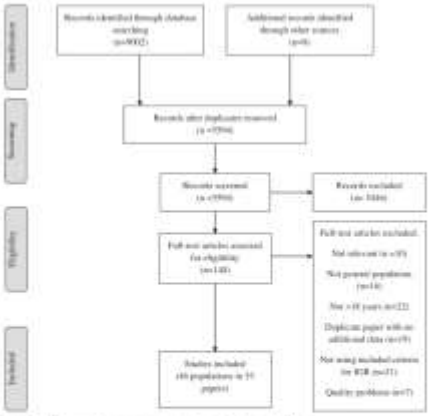

Figure 1 Flow diagram showing study selection

Quality of studies

The quality category assigned to each study is reported in Supplementary table S1. 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

Table 1 Mean prevalence of IGT by several moderator variables

Variable	k	N	Prevalence	95% CI	Q_b (df)	Q_w (df)	I^2 (%)
Age (year)							
18 and over	8	15 048	9.4	7.1–12.4	19.15 (2)*	198.58 (7)*	96.5
30–65	23	45 828	11.8	9.8–14.2		1077.06 (22)*	98
66+	4	2941	25.1	17.8–34.1		72.97 (3)*	95.9
Diagnostic criteria							
1. 2hPG 7.8–<11.1 mmol/l	2	2951	7.4	5.7–9.6	19.9 (3)*	3.86 (1)*	74.1
2. FPG < 8.0 mmol/l and 2hPG 8.0–<11.0 mmol/l	8	10 047	19.7	13.9–27.2		361.41 (7)*	98.1
3. FPG < 7.8 mmol/l and 2h 7.8–<11.1 mmol/l	19	43 722	10.3	8.6–12.2		704.38 (18)*	97.4
4. FPG < 7.0 mmol/l and 2hPG 7.8–<11.1 mmol/l	2	3678	13.9	7.6–24.2		49.83 (1)*	98
Quality category							
1—Higher	13	21 651	12.8	10.3–15.7	0.59 (2)	338.8 (12)*	96.5
2	12	25 686	11.5	9.3–14		370.82 (11)*	97
3—Lower	10	16 480	12.8	8–20		992.21 (9)*	99.1
Country							
Denmark	1	6784	12	11.2–12.8	43.46 (8)*	0.00 (0)	0.0
Finland	8	12 007	19.9	14.8–26.2		348.05 (7)*	98
Germany	2	3006	10.4	3.9–24.7		72.45 (1)*	98.6
Italy	3	3870	6.9	5.4–8.7		7.9 (2)*	74.7
Netherlands	1	2378	10.3	9.1–11.6		0.00 (0)	0.0
Portugal	1	5167	12.6	11.7–13.5		0.00 (0)	0.0
Spain	7	11 817	9.5	7.0–12.7		151.38 (6)*	96
Sweden	5	9849	14	8.1–23		329.68 (4)*	98.8
UK	7	9659	11.1	8.6–14.3		79.9 (6)*	92.5

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.
*: $P < 0.05$.

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.[30] 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[31,36,30] 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 1 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.

Table 2 Weighted multiple regression for IGT prevalence

Variable	β	95% CI	$Q_{(k)}$ (df)
Age(year)			
18 +	—	—	2.25 (2)
30–65	0.25	−0.28 to 1.01	
66+	0.72	−0.29 to 1.72	
Diagnostic criteria			
1) 2hPG 7.8–<11.1 mmol/l	0.49	−1.05 to 2.02	10.41 (3)*
2) FPG <8.0 mmol/l and 2hPG 8.0–<11.0 mmol/l	0.72	−0.29 to 1.72	
3) FPG < 7.8 mmol/l and 2hPG 7.8–<11.1 mmol/l	0.09	−0.94 to 1.12	
4) FPG < 7.0 mmol/l and 2hPG 7.8–<11.1 mmol/	—	—	
Country			
Denmark	0.81	−0.42 to 2.05	7.44 (8)
Finland	0.96**	−0.04 to 1.96	
Germany	0.65	−0.43 to 1.74	
Italy	—	—	
Netherlands	0.73	−0.88 to 2.34	
Portugal	1.12	−0.33 to 2.57	
Spain	0.53	−0.61 to 1.68	
Sweden	0.74	−0.25 to 1.74	
UK	0.38	−0.62 to 1.38	

Q_b, between study homogeneity statistic.
*: $P < 0.05$
**: Marginally significant $P = 0.0588$.

Sample age

The highest prevalence was found in samples aged 66 and over (25.1%; 17.8–34.1) followed by samples aged 30–65 (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

Table 3 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^2 (%)
Men							
Age (year)							
18 and over	6	5548	10	6.6–14.8	0.13 (2)	121.7 (5)*	95.9
30–65	7	8480	10.6	8.7–12.9		55.67 (6)*	89.2
66+	2	7385	8.9	2–3.2		298.06 (1)*	99.7
Diagnostic criteria							
1) FPG 5.6–6.9 mmol/l	2	2298	13	4.8–30.6	0.37(2)	56.13 (1)*	98.2
2) FPG 6.1–6.9 mmol/l	8	14 668	10.7	7.7–14.8		306.42 (7)*	97.7
3) FPG 6.1–6.9 and 2hPG < 7.8 mmol/l	4	3999	9.7	6.4–14.3		52.87 (3)*	94.3
Quality category							
1—Higher	6	6685	10.6	8.7–12.8	0.09 (2)	30.24 (5)*	83.5
2	5	8523	10.9	7.5–15.4		129.52 (4)*	96.9
3—Lower	4	6205	9.4	3.7–21.8		298.73 (3)*	99
Country							
Finland	2	2320	11.6	8.6–15.3	136.74 (8)*	6.39 (1)*	84.4
France	3	6177	7.5	3.6–14.9		111.53 (2)*	98.2
Germany	1	896	4.2	3.1–5.7		0.00 (0)	0.0
Greece	1	1514	20.5	18.5–22.6		0.00 (0)	0.0
Italy	1	2240	12.2	10.9–13.6		0.00 (0)	0.0
Netherlands	1	2378	12	10.8–13.4		0.00 (0)	0.0
Spain	2	752	6.1	1.9–18.4		15.4 (1)*	93.5
Sweden	1	359	10.6	7.8–14.2		0.00 (0)	0.0
UK	3	4777	14.4	11–18.8		14.64 (2)*	86.3
Variable	*k*	*N*	Prevalence		Q_b (df)	Q_W (df)	
Women							
Age (year)							
18 and over	6	6685	6.5	4.4–9.7	0.96 (2)	91.2 (5)*	94.5
30–65	6	6169	5.2	3.9–6.8		31.32 (5)*	84
66+	2	9287	7.3	1.1–35.9		477.71 (1)*	99.8
Diagnostic criteria							
1) FPG 5.6–6.9 mmol/l	7	14 610	7.2	3.9–13	1.27 (2)	549.58 (6)*	98.9
2) FPG 6.1–6.9 mmol/l	2	2846	6.5	1.8–20.8		62.61 (1)*	98.4
3) FPG 6.1–6.9 and 2hPG <7.8 mmol/l	4	4103	4.7	3.0–7.4		30.93 (3)*	90.3
Quality category							
1—Higher	5	4877	5.9	3.9–9.1	0.06 (2)	47.09 (4)*	91.5
2	5	8298	6.3	3.0–12.7		287.22 (4)*	98.6
3—Lower	4	8866	5.5	2.3–12.4		206.1 (3)*	98.5
Country							
Finland	2	2595	5.1	4.3–6	119.82 (7)*	0.12 (1)	0.0
France	3	8647	3.8	2.4–5.9		29.57 (2)*	93.2
Germany	1	757	1.9	1.1–3.2		0.00 (0)	0.0
Greece	1	1528	12	10.5–13.7		0.00 (0)	0.0
Italy	1	2497	9.9	8.8–11.1		0.00 (0)	0.0
Spain	2	967	4.7	1.9–11.3		9.46 (1)*	89.4
Sweden	1	382	6.3	4.3–9.2		0.00 (0)	0.0
UK	3	4771	10.6	5.6–19.2		58.12 (2)*	96.4

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.
*: $P<0.05$.

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 ($Q_{R(15)}=39.88$, $P<0.001$, see table 2 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 ($Q_{E(27)}=475.54$; $P<0.001$, $I^2=96.4\%$) meaning that there was still variability in the data that was not explained by the variables analysed.

Table 4 Mean prevalence of combined IGT and IFG by several moderator variables

Variable	*k*	*N*	Prevalence	95% CI	Q_B (df)	Q_W (df)	I^2 (%)
Age(year)							
18 and over	4	9959	3.5	2.5–4.7	7.94 (2)*	21.53 (3)*	86.1
30–65	6	14 605	1.9	1.5–2.5		24.88 (5)*	79.9
66+	1	499	2.7	1.6–4.6		0.00 (0)	0.0
Quality category							
1—Higher	2	6077	3.2	1.7–6	1.63 (2)	12.5 (1)*	92
2	3	5908	1.8	1–3.4		21.95 (2)*	90.9
3—Lower	6	13 080	2.6	1.9–3.6		42.26 (5)*	88.2
Country							
Finland	2	3217	1.9	1.1–3.4	15.12 (5)*	3.56 (1)*	71.9
Germany	1	1653	1.2	0.8–1.9		0.00 (0)	0.0
Italy	1	919	2.1	1.3–3.3		0.00 (0)	0.0
Portugal	1	5167	2.4	2–2.9		0.00 (0)	0.0
Spain	4	7882	3.4	2.5–4.7		19.79 (3)*	84.8
UK	2	6225	2.4	1.2–4.5		14.2 (1)*	93

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.
*: $P<0.05$.

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 3 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 ($Q_{(5)}=68.7$; $P<0.001$).

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 4 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 30–65 (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 S2 in 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 ($Q_{E(1)}$=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 <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 were 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 USA, 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 USA, 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 with women, higher prevalence of IGT but not IFG with increasing age and the higher prevalence of IGT compared with 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 with 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 IGT, IFG 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.

Supplementary data

Supplementary data are available at *EURPUB* online.

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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.

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Appendix 4

Supplementary file for publication 2 containing table 8.

Table 8: Characteristics of studies included in the review

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
Åberg, Sweden, 1995-1999	Prospective study of all singleton pregnant women in one geographical area	12,382	NR	NR	NR	NR	One step: 75g OGTT	27-28	GDM if 2 hour value of 9mmol/l or more	1.2% (1.0-1.4)	2
Alberico, Italy, 1997-2000	Prospective study of all pregnant women at one clinic	856	32.5	NR	61%	NR	Two step: those with positive GCT given 100g OGTT	24-28	GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to Carpenter and Coustan	6.6% (4.9-8.2)	3
Anderberg, Sweden, 1991-2003	Retrospective of all pregnant women in one	129,143	NR	NR	NR	NR	One step: 75g OGTT	28	GDM if 2 hour value of	1.2 (1.2-1.3)	1

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
	geographical area								9mmol/l or more		
Avalos, Ireland, 2007-2009	Retrospective study of all pregnant women at five clinics	5,500	32 (5.3)	26.9 (5.1)	NR	32% in 1st or 2nd degree	One step: 75g OGTT	24-28	OGTT interpreted according to IADPSG and WHO 2006	IADPSG: 12.4% (11.5-13.3) WHO 2006: 9.4% (8.7-10.2)	3
Breschi, Italy, 1988-1991	Prospective study of all pregnant women at one clinic	539	29.4 (4.6)	22.5 (3.3)	Mean: 1.7	34.2%	One step: 100g OGTT	Mean = 26	OGTT interpreted according to NDDG	3.2% (1.7-4.6)	3
Bugallo, Spain, 2004-2006	Retrospective study of all pregnant women at one hospital	11,628	30 (6)	NR	NR	NR	Two step: those with positive 50g GCT given 100g OGTT	24-28	GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to Carpenter and Coustan	6.4% (5.9-6.9)	1
Cauza, Austria, 1999-2001	Prospective study of all pregnant women at one hospital	2,421	NR	NR	NR	NR	One step: 75g OGTT	24-28	GDM if 1 hour value of 8.9mmol/l or more	8.6% (7.5-9.7)	3

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
Chevalier, France, 2002-2006	Prospective study of all pregnant women at one hospital	11,545	NR	NR	46%	NR	Two step: those with positive GCT given 100g OGTT	24-28	GCT of 7.2mmol/l or more positive. GDM diagnosed on basis of OGTT according to Carpenter and Coustan	4.3% (3.9-4.6)	1
Chico, Spain, 1999-2001	Retrospective study of all pregnant women at a set of clinics	6,428	NR	NR	NR	NR	Two step: those with positive GCT given 100g OGTT	24-28	GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to NDDG Carpenter and Coustan	NDDG: 6.5% (5.9-7.1) Carpenter and Coustan: 6.8% (6.1-7.4)	1
Coolen, Belgium, 2008	Prospective study of all pregnant women attending one clinic	317	30.6(0.3)	NR	33.9%	NR	Two step: those with positive GCT given 100g OGTT	24-28	GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to	3.2% (1.2-5.1)	1

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
Cordero, Spain, NR	Randomised controlled trial of pregnant women in one area.	156	32.9 (4.5)	23.6 (4)	47.4%	14.1% 1st degree and 32% 2nd degree.	Two step: those with positive GCT given 100g OGTT	24-28	Carpenter and Coustan GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to NDDG	8.3% (4-12.7)	2
Corrado, Italy, 1990	Retrospective study of all singleton pregnant women seen by 6 obstetricians	738	NR	NR	NR	NR	One step: 75g OGTT	24-28	OGTT interpreted according to IADPSG	11.9% (9.6-14.3)	1
Cosson, France, 2002	Prospective study of all singleton pregnant women at one hospital	2,111	29.2 (5.8)	23.4 (4.7)	Mean 2.08 (SD 1.37)	12.8%	One step: 75g OGTT	24-28	OGTT interpreted according if fasting value 5.3mmol/l or more (French recommendations) and/or 2 hour value of 7.8 mmol/l or	12.6% (11.1-14.0)	1

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
									more (according to WHO 1999).		
Di Cianni, Italy, 1995-2001	Retrospective study of all pregnant women at one clinic.	3,950	31.1 (4.7)	22.5 (3.7)	56.1%	17.1%	Two step: those with positive GCT given 100g OGTT	24-28	GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to Carpenter and Coustan	8.4% (7.6-9.3)	1
Duran, Spain, 2011-2012 cohort 1	Prospective study of all pregnant women at one hospital	1,750	32	Median 22.7	43.9%	8.4%	Two step: those with positive 50g GCT given 100g OGTT	24-28	GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to Carpenter and Coustan	10.6% (9.1-12.0)	1
Duran, Spain, 2012-2013 cohort 2	All pregnant women at one hospital	1,526	32	Median 22.8	44.7%	9.4%	One step: 75g OGTT	24-28	GDM diagnosed according to IADPSG	35.5% (33.1-37.9)	1

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
Fadl, Sweden, 1991-2003	Retrospective study of all singleton pregnant women in Sweden	1,260,297	NR	NR	42%	NR	Two step: those with positive RBG given 75g OGTT	NR	RBG of 8mmol/l or higher considered positive. GDM diagnosed on basis of 75g OGTT if fasting value 6.1mmol/l and/or 2 hour value of 9mmol/l or more.	0.84% (0.82-0.86)	1
Fedele, Italy, 1990-1991	Prospective study of all women attending family planning clinics in one area	490	NR	NR	NR	NR	Two step: those with positive 50g GCT given 100g OGTT	High risk women 10-14, 24-28 and 30-32. Others 24-28.	GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to Carpenter and Coustan	10.8% (8.1-13.6)	1

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
Griffin, Ireland, NR	All women attending one hospital randomised to selective or universal screening	1299	27.4 (5.6)	During pregnancy 28.2 (4)	39.3%	NR	Two step: those with positive 50g GCT given 100g OGTT	26-28	GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to Carpenter and Coustan	2.7% (1.8-3.6)	2
Ignell, Sweden, 2014	Retrospective study of all singleton pregnant women in two areas.	156,144	NR	NR	NR	NR	One step: 75g OGTT	28	GDM if 2 hour value of 9mmol/l or more	2.2% (2.1-2.3)	1
Janghornbani, UK, 1996-1997	Prospective study of all pregnant women screened in one area.	3,933	NR	NR	NR	NR	Two step: those with positive RBG given 75g OGTT	24-28	RBG of 6.5mmol/l or more positive. GDM diagnosed according to OGTT if 2 hour reading of 11mmol/l or more	1.7% (1.3-2.1)	1

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
Jiménez-Moleón, Spain, 1995	Retrospective study of all singleton pregnant women in one hospital.	1,962	NR	NR	NR	NR	Two step: those with positive GCT given 100g OGTT	24-28	GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to NDDG	3.3% (2.5-4.1)	1
Kayema-Kay, UK, 1996-1997	Prospective study of all singleton women at one hospital	1484	NR	NR	NR	NR	One step: 75g OGTT	24-28	GDM if 2 hour value of 9.0 mmol/l or more	1.2% (0.7-1.8	
Lacaria, Italy, 2012-2013	Prospective study of all pregnant women in two areas.	2497	33.5 (5)	22.8 (4)	NR	NR	One step: 75g OGTT	24-28	OGTT interpreted according to IADPSG	10.9%	1
Lind, UK, 1984	Prospective study of all singleton pregnant women in one clinic.	2,285	NR	NR	NR	NR	Two step: those with positive RBG given 75g OGTT	28-32	RBG greater than 4.3mmol/l to 6.4mmol/l (depending on time since meal) considered positive. GDM diagnosed on	0.3% (0.1-0.5)	1

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
									the basis of OGTT 2 hour value of 8.0mmol/l and above.		
Lindqvist, Sweden, 2011-2012	Population study of all pregnant women in areas where universal screening offered	20,822	30	25	NR	NR	One step: 75g OGTT	NR	GDM if 2 hour value over 10mmol/l	2.2% (2-2.4)	1
Malmqvist, Sweden, 1999-2005	Retrospective study of all singleton pregnant women in one area	81,110	30.4 (5)	NR	47.3%	NR	One step: 75g OGTT	28	GDM if 2 hour value over 10mmol/l	2% (1.9-2.1)	1
Meek, UK, 2004-2008	Retrospective study of all singleton pregnant women in one area	25,543	30.7(95% CI 30.6-30.8)	24.8 (95% CI 24.6-24.8)	38.7%	NR	Two step: those with positive GCT given 100g OGTT	26-28	GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of 75g OGTT interpreted	4.9% (4.6-5.2)	1

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
									according to IADPSG		
Miailhe, France, 2011-2012	Prospective study of all singleton pregnant women in one area	2,187	NR	36% with BMI >25	41.7%	NR	One step: 75g OGTT	24-28	GDM diagnosed according to IADPSG	14% (12.7-15.6)	1
Murgia, Italy, NR	Prospective study of pregnant women at one clinic	1,103	31 (5)	22.5 (3.8)	NR	14.2% 1st degree	Two step: those with positive GCT given 100g OGTT	16-18, 24-26 and 30-32	GCT of 7.2 mmol/l or more positive. GDM diagnosed on basis of OGTT according to Carpenter and Coustan	16-18: 6.6% (5.2-8.1 24-26: 5.8% (4.4-7.2) 30-32: 9.9% (8.1-11.6) Total: 22.4 (19.9-24.9)	1
Orecchio, Switzerland, 2004-2005	Prospective study of all singleton pregnant women at one hospital	1,042	NR	NR	NR	NR	Two step: those with positive GCT given 100g OGTT	24-28	GCT of 7.8 mmol/l or more positive. GDM diagnosed on basis of OGTT according to	4.8% (3.5-6.1)	1

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
Oriot, Belgium, 2009-2011, cohort 1	Retrospective study of all pregnant women at one hospital	1424	NR	NR	NR	NR	Two step: those with positive GCT given 100g OGTT.	24-28	Carpenter and Coustan GCT of 7.8mmol/l or more positive. GDM diagnosed on basis of OGTT according to Carpenter and Coustan	8.2% (6.8-9.6)	2
Oriot, Belgium, 2011-2012, cohort 2	Retrospective study of all pregnant women at one hospital	1206	NR	NR	NR	NR	One step: 75g OGTT	24-28	GDM diagnosed according to IADPSG	22.9% (20.5-25.3)	2
Östlund, Sweden, 1994-1996	Prospective study of all pregnant women in one area	3,616	27.9 (4.8)	23.8 (4.1)	46%	9.4%	One step: 75g OGTT	28-32	GDM diagnosed according to IADPSG	1.7% (1.3-2.1)	1
Pérez-Ferre, Spain, 2007-2008	Retrospective study of all pregnant	1,311	NR	NR	NR	NR	Two step: those with positive GCT given	24-28	GCT of 7.8mmol/l or more positive.	5.4% (4.5-7)	1

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
	women in one area						100g OGTT. Carbohydrate rich diet followed 3 days prior to OGTT.		GDM diagnosed on basis of OGTT according to Carpenter and Coustan		
Pintaudi, Italy, 2010-2011	Retrospective study of all pregnant women at one clinic	1,015	NR	NR	NR	NR	One step: 75g OGTT	24-28	GDM diagnosed according to IADPSG	11.1%	1
Pöyhönen-Alho, Finland, 1996-1998	Prospective study of pregnant women from one area	532	NR	NR	NR	NR	Two step: those with positive GCT given 100g OGTT.	28	GCT of 7.3mmol/l or more positive. GDM diagnosed on basis of OGTT with fasting values of 4.8mmol/l or more, 10mmol/l or more at 1 hour or 8.7mmol/l or more at 2 hour.	2.8% (1.4-4.2)	3

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
Ricart, Spain, 2002	Prospective study of all singleton pregnant women from 16 hospitals	9,270	NR	NR	NR	NR	Two step: those with positive GCT given 100g OGTT.	24-28	GCT of 7.8 mmol/l or more positive. GDM diagnosed on basis of OGTT according to NDDG	8.8% (8.3-9.4)	1
Rüetschi, Italy, 2010-2012	Retrospective study of all pregnant women in with OGTT data in laboratories in two areas	2,298	31	NR	NR	NR	One step: 75g OGTT	24-28	GDM diagnosed according to IADPSG	10.9% (9.7-12.3)	1
Sacks, UK, 2000-2006,	Prospective study of all pregnant women at two study centres	1671	NR	NR	NR	NR	One step: 75g OGTT	24-32	GDM diagnosed according to IADPSG	21.3% [20.1-22.6]	3
Vassilaki, Greece, 2007	Prospective study of singleton pregnant women from	1,122	NR	NR	NR	NR	One step: 75g OGTT	24-28	GDM diagnosed according to Carpenter and Coustan	9.1% (7.4-10.8)	2

First author, country, years data collected	Sampling Method	Sample Size	Mean Age (SD)	Mean BMI (SD)	Parity (% nulli-parous)	Family History	Screening Type	Gestation at testing (weeks)	Criteria Used (category)	Overall prevalence (95% CI)	Quality Score
	four clinics in one area										
Vignoles, France, 2006-2007	Retrospective study of all singleton pregnant women at one hospital	3,237	NR	NR	NR	NR	Two step: those with positive GCT given 100g OGTT.	34-32	GCT of 7.2 mmol/l or more positive. GDM diagnosed on basis of OGTT according to Carpenter and Coustan	5.1% (4.4-5.9)	1

Appendix 5

PDF of published manuscript for publication 2.

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Prevalence of gestational diabetes mellitus in Europe: A meta-analysis

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ABSTRACT

Aims: Estimates of the prevalence of gestational diabetes vary widely. It is important to have a clear understanding of the prevalence of this condition to be able to plan interventions and health care provision. This paper describes a meta-analysis of primary research data reporting the prevalence of gestational diabetes mellitus in the general pregnant population of developed countries in Europe.

Methods: Four electronic databases were systematically searched in May 2016. English language articles reporting gestational diabetes mellitus prevalence using universal screening in general pregnant population samples from developed countries in Europe were included. All papers identified by the search were screened by one author, and then half screened independently by a second author and half by a third author. Data were extracted by one author. 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 3258 abstracts were screened, with 40 studies included in the review. Overall prevalence of gestational diabetes mellitus was 5.4% (3.8–7.8). Maternal age, year of data collection, country, area of Europe, week of gestation at testing, and diagnostic criteria were found to have a significant univariate effect on GDM prevalence, and area, week of gestation at testing and year of data collection remained statistically significant in multivariate analysis. Quality category was significant in multivariate but not univariate analysis.

Conclusions: This meta-analysis shows prevalence of GDM that is at the upper end of previous estimates in Europe.

1. Introduction

Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance that is first diagnosed in pregnancy and increases the risk of complications for both mother and baby during pregnancy [1]. It is estimated that GDM affects around 7% of all pregnancies worldwide although prevalence is difficult to estimate as rates vary from study to study because of a lack of accepted diagnostic criteria and differences in screening procedures [2]. Some earlier diagnostic criteria were based on the criteria used in non-pregnant individuals and in others thresholds were created based on the predictive value of future type 2 diabetes in the mother. In recent years, there has been an increasing focus on diagnostic thresholds that

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predict the likelihood of adverse outcomes in pregnancy (HAPO) [3]. Adverse outcomes include macrosomia, shoulder dystocia and birth injury, primary caesarean delivery, preeclampsia, preterm delivery and foetal and neonatal mortality [4].

In addition to adverse outcomes during pregnancy and birth, the consequences of GDM extend beyond pregnancy with affected women having a seven fold increased risk of type 2 diabetes mellitus compared to women who have not had GDM. Rates of type 2 diabetes mellitus after a diagnosis of GDM vary depending on the population and length of follow up, but have been reported to be as high as 70% [5,6]. Women are thought to be at the greatest risk of developing type 2 diabetes mellitus in the first five years following a pregnancy with GDM, with incidence of type 2 diabetes mellitus plateauing at around 10 years [6].

Although women who have had GDM are at an increased risk of type 2 diabetes mellitus, research has shown that by making lifestyle changes they can prevent or delay progression to type 2 diabetes mellitus [7]. With prevalence of type 2 diabetes mellitus increasing rapidly, a diagnosis of GDM represents an opportunity for intervention to reduce the burden of type 2 diabetes mellitus [8]. This is why it is so 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. We have therefore conducted a meta-analysis of observational primary research studies that have assessed the prevalence of GDM in the general population of pregnant women in developed countries in Europe, regardless of the specific diagnostic criteria used. We have derived an overall prevalence estimate for GDM and examined moderator variables that potentially influenced this estimate. Although narrative reviews exist on this topic, this is the first systematic review and meta-analysis to bring together and synthesise all the evidence.

2. Material and methods

2.1. Literature search and study selection

A meta-analysis of primary research studies reporting prevalence of GDM was undertaken in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reviews [9]. A search was conducted in MEDLINE, CINAHL, Health Source and PsycInfo for articles published before June 2016. The following combination of search terms were used with each database: (prevalence or incidence) and (gestational diabetes or diabetes in pregnancy or gestational diabetes mellitus). Reference lists and citations of included papers were checked to identify any other potentially relevant papers but key authors and experts 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 all papers were screened by one author (CE). Independent screening of records was split between the two other authors, with JE screening half and DC screening the other half. The full texts of papers were retrieved for studies that were considered relevant, but also for those that contained insufficient information to allow judgement of relevance. These were checked against the inclusion criteria by CE and independently by JE. Reference lists of included articles were reviewed to identify any additional relevant articles. 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.

Papers were screened against the following inclusion criteria:

(1) Population: general population of pregnant women, living in a developed country in Europe (as defined by the Financial Times Stock Exchange).
(2) Outcome measure: prevalence of GDM diagnosed using universal screening carried out in the second or third trimester, using either a GTT alone or two step screening with glucose challenge test (GCT) followed by a GTT.
(3) Study design: observational study, published in English.

The review was limited to developed countries in Europe because of the wide differences in prevalence of type 2 diabetes mellitus and GDM between developed and developing countries [5,10]. This removed one potential source of heterogeneity in the review and also ensured its relevance 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 of pregnant women if it was drawn from a source that covered the majority of the population, such as population registers, general practice registers or registers of clinics for pregnant women (in countries where registration at general practices and clinics for pregnancy women 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 GDM (due to family history of type 2 diabetes mellitus, or lifestyle and medical factors) were excluded. Studies were excluded if the majority of the sample were immigrants and did not originate from an included developed country.

2.2. 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, type of screening/testing carried out and diagnostic criteria for

GDM. The outcome measures extracted were number and proportion of sample with GDM, and where reported the number and proportion of sample with GDM by different demographic factors such as age and Body Mass Index (BMI).

Where individual studies reported multiple prevalence estimates according to different diagnostic criteria, only one prevalence estimate was included in the meta-analysis to avoid dependency effects. The prevalence estimate deriving from the criteria that were most commonly used in other papers in the review was the one selected for inclusion in the meta-analysis so that the estimate would be 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.

2.3. Quality appraisal

The quality of included studies was assessed using a checklist based upon the example published by the Joanna Briggs Institute [12] 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 high, medium or low according to how likely they were to put the study at risk of bias. High risk weaknesses were those that put the study at high risk of bias or made the risk of bias difficult to assess, and 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 GDM. Medium risk weaknesses included low participation rate (50–70%), not reporting women's gestation at testing and sample size of less than 300. Low risk weaknesses included not reporting characteristics of the sample and not reporting differences between participants and non-participants.

Included studies were then given a quality rating as follows:

1: Only low risk weaknesses.
2: One medium or more than one low risk weakness.
3: One high risk or multiple medium risk weaknesses.

2.4. 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 GDM was transformed into a logit event rate effect size and the standard error associated with this was calculated [13]. The logits were retransformed to proportions after analysis to aid interpretation of the results. Combined effect sizes were calculated and analyses were carried out twice: both including and excluding outlying logit event rates. No significant differences were found between these analyses 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 [13]. In contrast, random effects models allow for the possibility that there are also random differences between studies that are not only due to sampling error but as a result of some other factor such as variation in procedures, measures or settings. The choice of the random effects model to combine studies in this meta-analysis was based upon literature on GDM prevalence which suggests that the variability in reported prevalence for GDM may be the result of the use of different methodologies and criteria [5].

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.

3. Results

3.1. Description of included studies

Fig. 1 shows a PRISMA flow diagram of studies identified by the search. The search identified 3258 abstracts of which 161 were potentially relevant after title and abstract screening. The full text articles were retrieved and assessed against the inclusion criteria, resulting in 40 included studies reported in 41 papers [14–53] (additional papers: [54]). These 40 studies included a total of 1,778,399 participants. The characteristics of the studies included in the review are presented in Table 1. Studies were conducted across 11 of the 17 countries defined as developed European countries: Italy ($n = 9$), Sweden ($n = 7$), Spain ($n = 7$), France ($n = 4$), UK ($n = 5$), Ireland ($n = 2$), Belgium ($n = 2$), Greece ($n = 1$), Finland ($n = 1$), Austria ($n = 1$), and Switzerland ($n = 1$). No additional papers were identified by manual searching of reference lists.

Around half of studies ($n = 22$) used a single step screening strategy where all women were given a GTT, and the others

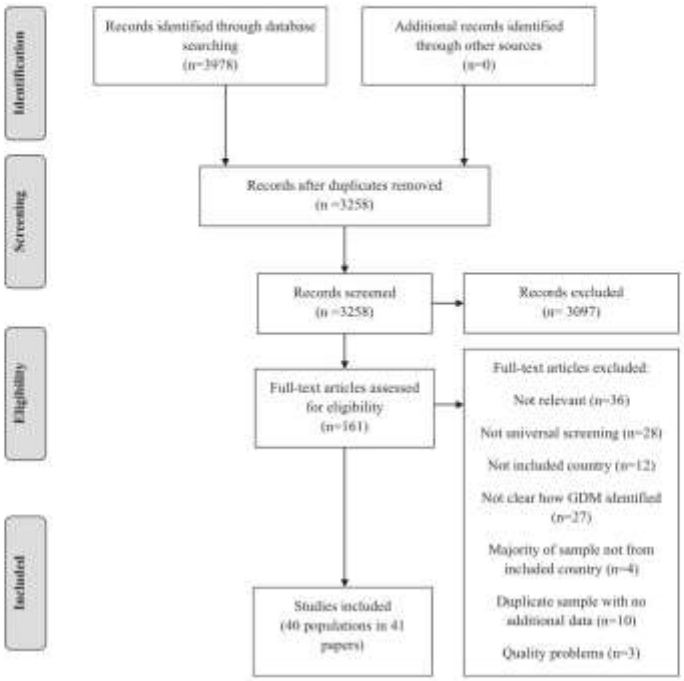

Fig. 1 – Flow diagram showing study selection.

used two-step screening, where all women were screened first with a GCT, then those with a positive GCT were given a GTT. Two studies used both one-step screening in one cohort, and two-step screening in a second separate cohort of women [28,53]. The most commonly used diagnostic criteria were Carpenter and Coustan [55] which were used to diagnose GDM in 14 studies as part of two-step screening and one study using one-step screening. The IADPSG criteria [56] were applied in a total of ten studies, of which nine used one-step screening and one used two-step screening. The NDDG [57] criteria were used in three studies using two-step screening and one study using one-step screening. A modification of the EASD criteria [58] that diagnosed GDM on the basis of two hour values only without assessing fasting blood glucose was used in four studies all using one step screening. Only three studies reported that they tested for and excluded any women with undiagnosed pre-existing diabetes that was uncovered in the first trimester.

3.2. *Quality of studies*

The quality category assigned to each study is reported in Table 1. Three studies were identified that had two major weaknesses [59–61]: in all three studies it was not clear if the study sample was a whole population of pregnant women and response rates were not reported. 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. The majority of included studies were classed as either the higher ($n = 23$) or middle quality category ($n = 11$) and therefore had only low or medium risk weaknesses. The remaining studies fell into the lower quality category ($n = 6$) and in addition to any low risk weaknesses also had weaknesses that put the study at higher risk of bias. These higher risk weaknesses included non-reporting of response rate ($n = 4$), not reporting where women were recruited from ($n = 1$) and very low participation rate ($n = 1$). Of the weaknesses categorised as low or medium risk, the most common problems were non-reporting of sample characteristics ($n = 21$), non-reporting of information on women who did not participate ($n = 17$), low participation rate ($n = 5$), and non-reporting of gestation at testing ($n = 2$).

3.3. *Analysis of outliers*

One outlier was identified that reported prevalence of 35.5% [28]. This figure was reported for a cohort of women with a median age of 32 and median pre-pregnancy BMI of 22.8 kg/m^2 and who were diagnosed with GDM through universal screening using IADSPG criteria. The majority of women

were Caucasian (62%) and only 2% had previous GDM. These characteristics are largely similar to those of other studies giving no clear explanation for the high prevalence found in this study.

3.4. Mean prevalence of GDM

The mean prevalence of GDM overall was 5.4% (95% CI: 3.8–7.8). The mean prevalence in studies using one-step screening was 6.4% (3.8–10.4) and 4.7% (2.7–8.1) in studies using two-step screening. There was no significant difference in prevalence of GDM between studies using one-step and two-step screening ($Q_{[1]} = 0.64$; $p = 0.424$). The analysis of homogeneity in the data with regards to type of screening showed variability within studies assessing prevalence using one-step screening ($Q_{[19]} = 13019.04$; $p < 0.001$) and those using two-step screening ($Q_{[21]}$=15517.54; $p < 0.001$).

3.5. Analysis of Moderators for GDM

As there was no significant difference in prevalence of GDM by screening type, the analysis of prevalence by moderator variables is presented in overall terms. Table 2 shows the individual effects of different categorical moderator variables. Sample age, diagnostic criteria, country the study was conducted in, year that data collection started and week of gestation at testing, all had a significant effect on the prevalence of GDM, whereas the quality category of studies, mean BMI, ethnicity, and family history of diabetes in samples, did not have a significant effect. There were too few studies reporting parity data for this variable to be included in analyses.

3.5.1. Sample age

Prevalence was higher in samples with a mean age of 30.8 years and over (9.6%; 6.7–13.7) compared to those with a mean age of 30.7 and under (4.3%; 2.3–8.0).

3.5.2. Diagnostic criteria

Analysis of the effect of diagnostic criteria on GDM prevalence found the highest prevalence estimate in studies using the IADPSG criteria (14.1%; 9–21.5; [56]), the second highest prevalence was found in studies using Carpenter and Coustan criteria (6.9%; 5.4–8.7; [55]). The second lowest prevalence estimate was in studies using the NDDG criteria (5.3%; 2.7–10; [62]) and the lowest estimate was for those that defined GDM using modified EASD criteria with two hour readings only (1.4%; 0.9–2.2).

3.5.3. Country

In the analysis by country, the highest prevalence was found in studies conducted in Italy (10%; 7.6–13) and the lowest in Sweden (1.5%; 1–2.3). Countries were sorted into three groups according to location in Europe: Northern Europe, Western Europe, Southern Europe. Highest prevalence was found in countries in Southern Europe (9.6%; 7.3–12.6) and lowest in Northern Europe (2.3%; 1.3–3.8).

3.5.4. Year

Estimates of GDM prevalence increased every decade with the lowest in the 1980s [0.9%; 0.1–10] and the highest in the 2010s (11.1%; 5.7–20.6).

3.5.5. Gestation at testing

The highest prevalence estimate for GDM was found in studies that screened for GDM at multiple time points in the second and third trimester (13.1%; 6.5–24.7) followed by those studies that tested participants between 24 and 28 weeks of gestation (7.5%; 5.9–9.4). The lowest prevalence estimate was in a study that screened for GDM at 28–32 weeks gestation (1.7%; 1.3–2.2). However, as this category only contained a single study this result must be interpreted with caution. The second lowest prevalence estimate was found in studies that screened only at 28 weeks of gestation (1.9%; 1.5–2.5).

3.5.6. Multivariate analysis

A weighted multiple regression was performed in order to explore which variables made the greatest contribution to the variability in prevalence of GDM. All variables explored in the univariate analysis were initially entered into the model except for sample age and mean BMI as there were too few studies reporting these variables for them to be included in the multivariate analysis. Correlations between different variables were explored and used to inform the selection of variables for the multiple regression. A moderate correlation was found between year of data collection and diagnostic criteria ($r = 0.478$; $p = 0.010$; $n = 28$). The variable diagnostic criteria could not be included in the multiple regression because of collinearity with this and other variables.

The final model included the following variables: quality category, type of screening (one or two step), gestation at testing, year data collection started and area of Europe. These variables accounted for 83% of total observed variability ($Q_{R[11]} = 125.6$, $p < 0.001$, see Table 3 for full results). All three of the variables that were significant in univariate analyses [area, gestation at testing and year of data collection] remained statistically significant when the other variables were held constant. Quality category and type of screening were not significant in univariate analysis but were significant in the multiple regression. However, the residual model was also statistically significant ($Q_{R[23]} = 1134.95$; $p < 0.001$, $I^2 = 98.0\%$) meaning that there was still variability in the data that was not explained by the variables analysed.

4. Discussion

This meta-analysis of 1,770,63 participants in 40 studies reported mean prevalence of GDM of 5.4%. No differences were found in prevalence estimates of GDM according to the type of screening used (one-step or two-step), mean BMI, ethnicity and family history. An increase in prevalence was found with increasing sample age and year of data collection. Diagnostic criteria, country and week of gestation at testing were also found to have an effect on GDM prevalence. Nevertheless, given the changing migration patterns across Europe, this prevalence estimate may well change in the future.

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

Table 2 – Mean prevalence of GDM by several moderator variables.

Variable	k	n	Prevalence	95% CI	Q_B (df)	Q_W (df)	I^2 (%)
Mean age (years)							
30.7 and below	9	122,648	4.3%	2.3–8.0	4.75 [1]*	2312.38 [8]*	99.7
30.8 and above	9	43,327	9.6%	6.7–13.7		806.49 [8]*	99
Diagnostic criteria							
NDDG	4	11,927	5.3%	2.7–10	60.1 [3]*	79.13 [3]*	96.2
Carpenter Coustan	15	47,502	6.9%	5.4–8.7		621.28 [14]*	97.7
EASD 2 h only	4	299,153	1.4%	0.9–2.2		420.48 [3]*	99.3
IADPSG	10	46,557	14.1%	8.9–21.5		2275.49 [9]*	99.6
Quality category							
1 – Higher	24	325,888	6.0%	4.1–8.5	3.0 [2]	7999.56 [21]*	99.7
2	12	1,442,4833	3.9%	2.2–7.1		6869.37 [11]*	99.8
3 – Lower	6	13,895	7.6%	4.8–12.0		366.60 [5]*	98.6
Country							
Austria	1	2421	8.6%	7.5–9.8	101.96 [10]*	0.00 [0]	0.0
Belgium	3	2497	9%	3.3–22.2		133.24 [2]*	98.5
Finland	1	532	2.8%	1.7–4.6		0.00 [0]	0.0
France	4	19,080	8%	4.1–14.9		403.18 [3]*	99.26
Greece	1	1122	9.1%	7.5–10.9		0.00 [0]	0.0
Ireland	2	6799	5.9%	1.3–23.8		85.59 [1]*	9.8
Italy	9	13,486	10%	7.6–13		210.45 [8]*	96.2
Spain	8	34,031	8.6%	5.1–14.1		1259.12 [7]*	99.4
Sweden	7	1,663,514	1.5%	1–2.3		3335.68 [6]*	99.8
Switzerland	1	1042	4.8%	3.7–6.3		0.00 [0]	0.0
UK	5	37,292	2.4%	0.8–7.0		1519.62 [4]*	99.7
Area of Europe							
Northern	15	1,708,137	2.3%	1.3–3.8	24.32 [2]*	14880.94 [14]*	99.9
Western	9	26,346	7.3%	4.6–11.3		651.79 [8]*	98.8
Southern	18	47,783	9.6%	7.3–12.6		1530.48 [17]*	98.9
Year data collection started							
1980–1989	2	2824	0.9%	0.1–10	14.95 [3]*	27.77 [1]*	96.4
1990–1999	14	1,508,604	2.9%	1.9–4.5		5500.94 [13]*	99.8
2000–2009	13	233,199	6.9%	4.3–10.8		5434.77 [12]*	99.8
2010–2016	9	34,343	11.1%	5.7–20.6		2187.66 [8]*	99.6
% Sample with family history of diabetes							
14% and below	5	10,106	12%	5.2–25.3	0.971 [1]	804.53 [4]*	99.5
15% and over	3	9989	7.6%	4.9–11.5		65.3 [2]*	96.9
% Sample Caucasian							
79% and below	2	3276	20.3%	5.4–53.6	2.73 [1]	265.93 [1]*	99.6
80% and over	7	102,821	5.5%	2.4–12.3		3040.83 [6]*	99.8
Gestation at testing							
24–28 weeks	28	105,096	7.5%	5.9–9.4	104.85 [3]*	2841.69 [27]*	99.1
28 weeks	6	381,273	1.9%	1.5–2.5		449.79 [5]*	98.9
28–32 weeks	1	3616	1.7%	1.3–2.2		0.00 [0]	0.0
Multiple time points	4	8877	13.1%	6.5–24.7		367.84 [3]*	99.2
Mean BMI							
20–24.9	10	19,131	9.8%	5.5–16.9	0.39 [1]	1062.55 [7]*	99.3
25–29.9	2	6799	5.9%	1.3–23.8		85.59 [1]*	98.8

* $p < 0.05$; 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.

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 with coverage of the majority of the pregnant population (e.g. clinic register) using appropriate methods (e.g. whole population). The majority of included studies had good participation rates. Only four studies had participation rates of 50–70% and only

Table 3 – Weighted multiple regression for GDM prevalence.

	β	95% CI	Q_{BS} (df)
Quality category			
1 – Higher	–	–	14.85 [2]*
2	0.042	−0.35 to 0.44	
3 – Lower	0.97*	0.47–1.47	
Area of Europe			
North	–	–	18.07 [2]*
West	0.54*	0.02–1.06	
South	1.04*	0.54–1.53	
Year data collection started			
1980–1989	–	–	29.03 [3]*
1990–1999	1.85*	0.71–3.0	
2000–2009	2.37*	1.21–3.52	
2010–2016	2.74*	1.61–3.88	
Gestation at testing			
24–28 weeks	0.49	−0.54 to 1.52	9.58 [3]*
28 weeks	−0.15	−1.11 to 0.83	
28–32 weeks	–	–	
Multiple time points	1.03	−0.11 to 2.17	
Type of screening			
One step	–	–	
Two step	−0.41*	−0.77 to 0.04	

* $p < 0.05$; Q_{BS}: between study homogeneity statistic.

one study had a very low participation rate of less than 50%. This allows us to be reasonably confident that the included studies used samples that were representative of the general pregnant population. Quality category of the study was not found to have any significant effect on prevalence of GDM in univariate analysis but was significant in the multiple regression.

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 GDM prevalence was also made difficult by heterogeneity in approaches to sampling, methods used to collect blood samples and the criteria used to define GDM.

The way GDM is defined makes it difficult to differentiate between pre-existing undiagnosed diabetes and GDM. The IADPSG guidelines suggest that all women or those at high risk have either fasting blood glucose, A1c or random blood glucose measured at the first prenatal visit and overt diabetes diagnosed if fasting blood glucose is 126 mg/dl or higher or A1c 6.5% or higher [56]. Only three of the studies included in the present review reported that they tested for pre-existing undiagnosed diabetes in this way and excluded any women meeting the criteria. Of these three studies two reported the number of women thus identified and in both the prevalence was very low at 0.1% and 0.5%. Similarly, analysis of the national health and nutrition examination survey carried out between 1999 and 2010 in the United States showed that approximately 0.5% of women of non-pregnant women of reproductive age had undiagnosed diabetes [63]. Therefore, although estimates of GDM may be inflated by the potential inclusion of women with undiagnosed pre-existing diabetes, given the low prevalence of this it is unlikely that the effect on GDM estimates would be large.

The ADA guidelines estimate that around 7% of pregnant women will be diagnosed with GDM [2] and a review by of GDM prevalence in Europe reported rates of between 2% and 6% [1]. This estimate of 2–6% was based on studies using both risk-based and universal screening, whereas our estimate of 5% was based only upon studies using universal screening which identifies more women with GDM than risk-based screening [16,42].

The specific diagnostic criteria was found to have a significant effect on prevalence estimates in this review, with the IADPSG [56] criteria giving the highest estimates and a modified EASD [58] and Carpenter Coustan [55] giving the lowest estimates. In contrast, the review by Buckley et al. [1,63] reported no consistent trend in prevalence according to diagnostic criteria. The IADPSG criteria were proposed on the basis of evidence from the HAPO study on the relationship between maternal hyperglycaemia and adverse outcomes. A number of associations, including the ADA, have adopted these recommendations while others have argued that they will increase prevalence without necessarily improving outcomes. A study by Duran et al. [26] has since shown that while using the IADPSG criteria does increases GDM prevalence, it also results in significant improvements in pregnancy outcomes. This study reported increases in prevalence of 3.5 times compared to Carpenter and Coustan criteria whereas we found rates according to IADPSG criteria to be around double Carpenter and Coustan.

The present review confirmed previous research showing that GDM prevalence increases with increasing maternal age and is higher in Southern and Western Europe compared to Northern Europe [1]. We did not find any effect for BMI, ethnicity or family history, but there were few studies that measured or reported these variables so there may have been insufficient power to detect any differences. A strength of the present study is that pooling studies using meta-analysis allows trends to be identified when there are inconsistencies between individual studies.

With GDM being closely linked to type 2 diabetes mellitus and sharing some risk factors, we would expect to see an increase in GDM over time [1]. Although we found significant increases in GDM prevalence over time, year of data collection was moderately correlated with diagnostic criteria. The IADPSG criteria were associated with the highest prevalence estimates for GDM but were also the criteria published most recently. It was not possible to enter diagnostic criteria into the multivariate analysis which makes it difficult to assess how much of the increase in prevalence over time was related to the widening of diagnostic criteria and how much it reflected true increases in prevalence. Increases in screening over time also makes interpreting trend in prevalence difficult [64], although by including only studies using universal screening this source of heterogeneity was removed from this review.

In summary, this is the first meta-analysis to bring together all the relevant evidence relating to GDM prevalence in Europe and to make sense of disparate findings. In the general population of developed Europe, around 1 in 20 pregnant women meet the criteria for GDM. These figures provide a

basis for the planning of interventions and health care provision for the prevention of type 2 diabetes mellitus. 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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Conflict of interest

None declared.

Contribution to authorship

CE designed the study, assisted with screening of data, conducted data extraction, performed analyses and drafted the manuscript. JE assisted with screening papers, analyses and drafting the manuscript. DC assisted with screening papers, analyses and drafting the manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2017.03.030.

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Appendix 6

PDF of published manuscript for publication 3.

DIABETES RESEARCH AND CLINICAL PRACTICE 104 (2014) e16–e19

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International Diabetes Federation

Brief report

Incidence of impaired glucose regulation and progression to type 2 diabetes mellitus in the Tayside region of Scotland

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ABSTRACT

This study assessed incidence of impaired glucose regulation (IGR) and progression to type 2 diabetes (T2D) in adults in one region of Scotland using routinely collected health-care data. Incidence of IGR was 2720 per 100,000 person years. Nine percent of IGR patients progressed to T2D in a mean time of 34 months.

1. 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 criteria for T2D. These two states of impaired glucose regulation (IGR) confer an increased risk of developing T2D [1]. Research has shown that progression from IGR to T2D can be prevented through lifestyle changes meaning that a diagnosis of IGR could offer an ideal opportunity to deliver preventative interventions [2]. In order to assess the feasibility of an intervention with IGR patients it is important to assess the rate of identification of IGR by health care providers and to characterise progression to T2D. Recent research in the United States has reported prevalence rates of IGR in the general population as high as 35% [3]. There has been little research on this topic conducted in the United Kingdom. The present study assess incidence of IGR and characterises progression from IGR to T2D in adults in one region in Scotland using routinely collected health-care data.

2. Materials and methods

2.1. Study design

The study adopted an observational retrospective cohort design using anonymised patient data for the complete population of Tayside, Scotland, UK (approx. population 400,000). Data were provided by the Health Informatics Centre (HIC) at the University of Dundee, and the main data set used

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was SCI-DC which is a validated diabetes clinical information system [4].

2.2. Population

HIC provided patient demographic information (i.e. gender, date of birth, and deprivation from the Scottish Index of Multiple Deprivation; [5]) and all instances of blood glucose testing in the population of Tayside from January 2003 to December 2008. This totalled 2,119,177 tests after excluding non-valid records (e.g. damaged samples). Patients were classified as having IGT or IFG if they had undergone two blood glucose tests on the same date (one coded in the records as a fasting test with the second test assumed to be carried out after an oral glucose tolerance test) that met the WHO [6] criteria for IGT and IFG (IGT: first test <7.0 mmol/l and second test 7.8–11.0 mmol/l; IFG: first test 6.1–6.9 mmol/l; second test <7.8 mmol/l). However, the majority of patients were found to have only taken a fasting test. Although the WHO criteria allow a single fasting test to be used to diagnose IFG, it also states that this classification is uncertain. In order to avoid loss of relevant data, patients with only one fasting glucose test of 6.0–6.9 mmol/l were classified as having undefined IGR (uIGR). Patients meeting any of the above criteria for IGR were included in the study if aged 18 and over with no previous diagnosis of T2D. Fig. 1 illustrates selection of patients in the study. Patients with IGR were followed up for diagnosis of T2D using the SCI-DC database which held complete data up to December 2011. Patients with T2D are defined as those who are diagnosed with diabetes over the age of 35 years, or younger patients for whom there is no immediate requirement for insulin.

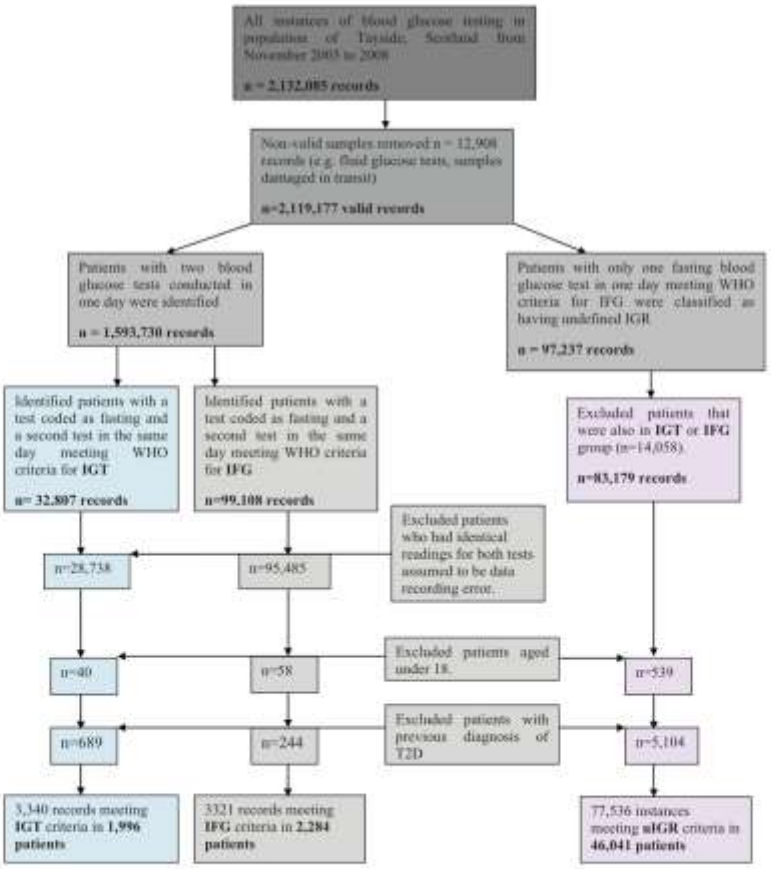

Fig. 1 – The identification of participants with impaired glucose regulation from the biochemistry data supplied by the Health Informatics Centre.

Table 1 – Hazard ratio of developing T2D in patients with all type of IGR according to sex, age, deprivation category and type of IGR.

		Univariate			Multivariate	
	No. (%) progressing to T2D	Mean time to progress (months)	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Sex						
Women	2114 (8.2)	33.9	1.00		1.00	
Men	2408 (10.2)	34.4	1.26 (1.19–1.34)	<0.001	1.1 (1.04–1.17)	0.002
Age at diagnosis of IGR						
18–27	14 (1.2)	30.9	1.00		1.00	
28–37	62 (2.5)	14.2	2.16 (1.21–3.87)	0.009	2.14 (1.2–3.83)	0.010
38–47	330 (8.0)	38.6	6.89 (4.03–11.75)	<0.001	6.73 (3.94–11.49)	<0.001
48–57	794 (12.0)	35.5	10.6 (6.24–17.97)	<0.001	10.21 (6.02–17.32)	<0.001
58–67	1320 (13.5)	35.2	12.01 (7.1–20.33)	<0.001	11.62 (6.86–19.67)	<0.001
68–77	1289 (11.9)	33.4	10.26 (6.06–17.37)	<0.001	9.96 (5.89–16.87)	<0.001
78–87	629 (6.2)	30.6	5.25 (3.09–8.92)	<0.001	5.14 (3.02–8.72)	<0.001
88 plus	84 (2.0)	22.3	1.68 (0.95–2.95)	0.072	1.68 (0.96–2.95)	0.072
Deprivation Category						
5 least deprived	752 (8.3)	35.1	1.00		1.00	
4	1315 (8.5)	34.8	1.2 (1.09–1.33)	<0.001	1.18 (1.07–1.31)	0.001
3	820 (9.4)	33.2	1.19 (1.08–1.32)	0.001	1.21 (1.01–1.34)	<0.001
2	775 (9.8)	34.8	1.14 (1.14–1.04)	0.008	1.15 (1.04–1.27)	0.006
1 most deprived	794 (9.9)	32.3	1.03 (0.94–1.12)	0.569	1.04 (0.95–1.13)	0.431
Type of IGR						
IGT	247 (12.6)	28.5	1.00		1.00	
IFG	182 (8.1)	33.4	1.38 (1.21–1.56)	<0.001	1.38 (1.21–1.57)	<0.001
uIGR	4093 (9.1)	34.5	0.88 (0.76–1.02)	0.082	0.88 (0.76–1.03)	0.106

The precise glucose levels used to diagnose T2D depend upon the criteria used at the time of diagnosis.

2.3. Analysis

Incidence rates of IGT, IFG and uIGR were calculated by dividing the number of new cases in one year by the population of Tayside aged over 18 in the same year. The relationship between potential risk factors and development of T2D was assessed by univariate and multivariate Cox regression, from which hazard ratios (HRs) and 95% CIs were calculated. Age, gender, deprivation category and type of IGR were entered as independent variables, with diagnosis of T2D as the dependent variable. Statistical analyses were carried out using SPSS for Windows version 19. Ethical approval was obtained from the School of Nursing, Midwifery and Health at the University of Stirling. The Tayside Committee for Medical Research Ethics have granted approval for studies using routinely collected, anonymised health data.

3. Results

3.1. Incidence of IGR

In total 50,321 patients were identified who met the criteria for either IFG ($n = 2284$), IGT ($n = 1996$) or uIGR ($n = 46,041$) during the study period (2003–2008). Of the 50,321 patients identified, 52.3% were female and the mean age at diagnosis was 62.8 (SD = 17.2). The total incidence across the study period was 2720 per 100,000 person years.

No significant differences were found in incidence of all types of IGR by gender ($t_{(10)} = 0.253$, $p = 0.897$) or deprivation category ($F_{(4)} = 0.21$, $p = 0.930$). Incidence differed significantly by age category ($F_{(3)} = 39.44$, $p < 0.001$) with a steady increase in incidence noted with increasing age.

3.2. Progression to T2D

A total of 4548 patients with IGR (9%) were diagnosed with T2D during the study with a mean time of 34 months between IGR and T2D diagnosis. Table 1 shows that men with IGR were at a small but significantly increased risk of developing T2D compared to women, as were more deprived patients compared to the least deprived. The risk of progression to T2D increased with increasing age. Patients with IGT were found to be at a small but significantly increased risk of developing T2D compared to those with IFG or uIGR. These associations were evident in univariate and multivariate analyses. Mean time for progression from IGR to T2D was largely similar in high-risk groups of patients, as for all patients who developed T2D in the study.

4. Discussion

To the best of our knowledge this study is the first to investigate the incidence of IGR and progression to T2D in the UK. We found that a considerable number of people were diagnosed with IGR over the study period, of whom nearly 10% of developed T2D within a relatively short time frame. However, a mean time of nearly three years between diagnosis of IGR and T2D does provide sufficient opportunity for an intervention to be delivered and lifestyle changes to be made. Those people with IGR at the highest risk of developing T2D are those with IGT and from a deprived background: as such,

these patients should arguably be prioritised within prevention programmes. The use of routinely collected patient data means that the rates of IGR reported here may not be reflective of the true rates in the general population. However, this methodology gives the findings greater clinical relevance which is of the highest importance if interventions are to be developed for use in this setting.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

We thank the staff of the Health Informatics Centre who provided data. Claire Eades was primarily responsible for gaining access to the data, analysis and drafting the manuscript and is the guarantor for the paper. Both Dr Graham Leese and Dr Josie Evans assisted in the analysis and drafting of the manuscript.

This study was funded by the School of Nursing, Midwifery and Health at the University of Stirling.

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Appendix 7

School of Nursing, Midwifery and Health Research Ethics Committee approval letter for publication 3.

JP/SG

12 October 2011

UNIVERSITY OF STIRLING

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Dear Claire

Progression from gestational diabetes and impaired glucose regulation to type 2 diabetes

Thank you for submitting your proposal to SREC. I am happy to inform you that the Committee has approved your application.

Three brief comments...

The application refer to an appendix contain a spreadsheet. This was not in fact appended, and I would be grateful if you could let me have a copy for our records.

Unless we have misunderstood something, the "Aims" section refers to the incidence of IGR over a ten year period, while the "Population and Sample" section refers to a 12-year period. It might be useful to clarify this.

Finally, I wonder whether the new classification of Type 1.5 (which now applies to a proportion of former Type 2 patients) makes a difference to the study. Is it not possible that, in the IGR arm at least, Type 2 and Type 1.5 patients will be conflated? Should not the regression equations take account of this possibility? This is an observation or query, rather than anything that counts as a condition of approval or a request for clarification.

Yours sincerely,

John Paley
(Chair)
School of Nursing, Midwifery and Health Research Ethics Committee

Appendix 8

NHS Tayside research and development approval letter for publication 3.

NHS Tayside

13 October 2011

Ms Claire Eades
Clinical Academic Fellow
School of Nursing Midwifery and Health
University of Stirling
STIRLING
FK9 4LA

Dear Ms Eades,

R & D MANAGEMENT APPROVAL – TAYSIDE

Title: Progression from gestational diabetes and impaired glucose regulation to Type 2 diabetes.

Chief Investigator: Ms Claire Eades **Local Collaborator: Professor Graham Leese**

Tayside Ref: 2011DM16* **NRS Ref: N/A**

REC Ref: N/A

Sponsor: University of Dundee

Funder: Unfunded

Many thanks for your application to carry out the above project here in NHS Tayside. I am pleased to confirm that the project documentation (as outlined below) has been reviewed, registered and Management Approval has been granted for the study to proceed locally in Tayside.

Approval is granted on the following conditions:-

- ALL Research must be carried out in compliance with the Research Governance Framework for Health & Community Care, Health & Safety Regulations, data protection principles, statutory legislation and in accordance with Good Clinical Practice (GCP).
- All amendments to be notified to TASC R & D Office.
- All local researchers must hold either a Substantive Contract, Honorary Research Contract, Honorary Clinical Contract or Letter of Access with NHS Tayside where required (http://www.nihr.ac.uk/systems/Pages/systems_research_passports.aspx).
- TASC R & D Office to be informed of change in Principal Investigator, Chief Investigator or any additional research personnel locally.
- Notification to TASC R & D Office of any change in funding.
- As custodian of the information collated during this research project you are responsible for ensuring the security of all personal information collected in line with NHS Scotland IT Security Policies, until destruction of this data.
- Recruitment numbers on a quarterly basis to be reported to TASC R & D Office.

Version 2 – 26/11/10

- Annual reports are required to be submitted to TASC R & D Office with the first report due 12 months from date of issue of this management approval letter and at yearly intervals until completion of the study.
- Notification of early termination within 15 days or End of Trial within 90 days followed by End of Trial Report within 1 year to TASC R & D Office.
- You may be required to assist with and provide information in regard to audit and monitoring of study.

Please note you are required to adhere to the conditions, if not, NHS management approval may be withdrawn for the study.

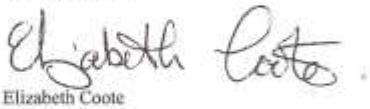
Approved Documents

Document	Version	Date
Protocol	1	07/10/11
Sponsor Letter – HIC Data Projects (University of Dundee)		06/03/09
Ethics Letter – HIC Data Projects		18/06/09

May I take this opportunity to wish you every success with your project.

Please do not hesitate to contact TASC R & D Office should you require further assistance.

Yours sincerely



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Appendix 9

PDF of published manuscript for publication 4.

Eades et al. BMC Pregnancy and Childbirth (2015) 15:11
DOI 10.1186/s12884-015-0457-8

BMC Pregnancy & Childbirth

RESEARCH ARTICLE Open Access

Progression from gestational diabetes to type 2 diabetes in one region of Scotland: an observational follow-up study

Claire E Eades[1*], Maggie Styles[1], Graham P Leese[2], Helen Cheyne[3] and Josie MM Evans[1]

Abstract

Background: The aim of this study was to investigate long-term risk of type 2 diabetes (T2D) following a diagnosis of gestational diabetes and to identify factors that were associated with increased risk of T2D.

Methods: An observational cohort design was used, following up all women diagnosed with gestational diabetes mellitus (GDM) attending a Diabetes Antenatal Clinic in the Dundee and Angus region of Scotland between 1994 and 2004 for a subsequent diagnosis of T2D, as recorded on SCI-DC (a comprehensive diabetes clinical information system).

Results: There were 164 women in the study who were followed up until 2012. One quarter developed T2D after a pregnancy with GDM in a mean time period of around eight years. Factors associated with a higher risk of developing T2D after GDM were increased weight during pregnancy, use of insulin during pregnancy, higher glycated haemoglobin (HbA1c) levels at diagnosis of GDM, and fasting blood glucose.

Conclusions: These findings suggest there is a viable time window to prevent progression from GDM to T2D and highlights those women who are at the greatest risk and should therefore be prioritised for preventative intervention.

Keywords: Gestational diabetes, Type 2 diabetes, Follow-up, United Kingdom

Background

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that begins or is first detected during pregnancy. GDM can have health consequences for the mother and baby both in the short and longer term. Although normal glucose regulation usually returns shortly after delivery, women diagnosed with GDM have at least a seven fold increased risk of developing Type 2 diabetes (T2D) in the future [1]. In Europe, GDM affects between 2-6% of pregnancies but research has shown that the incidence of GDM has been rising [2,3].

T2D is a growing public health concern associated with a number of serious health complications that reduce both the life-expectancy and quality of life of sufferers [4,5]. There is good evidence to suggest that lifestyle interventions targeted at those at high risk of T2D, such as those with pre-diabetes, can prevent or at least delay the onset of T2D [6]. A diagnosis of GDM therefore represents a window of opportunity for preventative intervention. However, there has been little research on interventions designed specifically for women with GDM, and none in the UK to our knowledge. In order to be able to assess the feasibility and practicality of a lifestyle intervention targeted at women with GDM, it is important to establish the nature of the progression from GDM to T2D in the UK context. A systematic review of studies assessing the association between GDM and T2D did not report any research that had been conducted in the United Kingdom [7]. This study therefore characterises the progression of GDM to T2D in the Dundee and Angus region of Scotland, UK.

Methods

Study design and population

This observational study used historical routinely collected health-care data to follow up women diagnosed with GDM. Antenatal care is a universal service accessed

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by almost all pregnant women in Scotland. Women diagnosed with GDM during routine antenatal care in the Dundee and Angus region (approximate population 250,000) attend the Diabetes Antenatal Clinic at Ninewells Hospital in the city of Dundee. All women in Dundee and Angus were screened with a fasting blood glucose (FBG) or random blood glucose (RBG) at 28 weeks gestation. All patients with any abnormal result (RBG of >5.5 mmol/l^{-1} two or more hours after food or >7.0mmo/l^{-1} within two hours of food; FBG >5.5 mmol/l^{-1}), any glycosuria and all high risk pregnancies underwent a 75 g oral glucose tolerance test (OGTT). All women diagnosed with GDM who had attended this clinic between 1994 and 2004, and who had no previous diagnosis of Type 1 or Type 2 diabetes were included in this study. Women diagnosed with GDM in the first trimester of pregnancy were excluded as these women were likely to have had undiagnosed pregestational diabetes [8]. GDM was diagnosed on the basis of clinical guidance in use at the time of the study which suggested an FBG of greater than 5.5 mmol/l^{-1}or a blood glucose reading two hours (2 h BG) after an OGTT of greater than 9 mmol/l^{-1}.

Data were extracted from paper based case records held at Ninewells Hospital containing clinical and personal data for all women who had attended the diabetes antenatal clinic between 1994 and 2004. These records included the following forms: a booking form which was completed at the first visit to the clinic after a diagnosis of GDM; follow up forms for each further visit to the clinic and a postnatal form containing information from a postnatal check-up. The information extracted from these forms included the mother's date of birth, family history of diabetes, history of GDM in a previous pregnancy, parity, birth weight of previous babies, week of gestation, OGTT fasting and 2 hour blood glucose levels at booking and postnatal (where recorded), mother's weight, Hba1C and treatment during pregnancy. Week of gestation, mother's weight and HbA1c were extracted from the booking, follow up and postnatal forms where recorded.

Data extracted from the paper based records were anonymised and linked to SCI-DC, a validated diabetes clinical information system [9], by the Health Informatics Centre at the University of Dundee (HIC). Patients were followed up for a diagnosis of T2D using the Scottish Care Information – Diabetes Collaboration (SCI-DC) system which holds complete information on patients diagnosed with T2D in Scotland up to March 2012. Women who died or migrated out of the health board during the follow up were not excluded from the study but the date of death/migration was used as their study end date in the analysis.

Patients with T2D are defined as those who are diagnosed with diabetes over the age of 35 years, or younger patients for whom there is no immediate requirement for insulin. World Health Organisation (WHO) criteria were used to diagnose T2D but the precise glucose levels used depended upon the criteria in use at the time of diagnosis. The majority of women included in the study (97%) were diagnosed using the WHO criteria published in 1999 [10] which defines T2D on the basis of a fasting plasma venous sample of 7.0 mmol/l^{-1} or higher and a 2 hour post OGTT value of 11.1 mmol/l^{-1}. The remainder were diagnosed using the WHO 1985 criteria [11] which had a higher value for fasting venous plasma of 7.8 mmol/l^{-1} or higher but the same 2 hour value. The data were also linked to a portion of the ISD SMR02 dataset which provided demographic information not available from paper based records such as deprivation category (from the Scottish Index of Multiple Deprivation [12] and body mass index (BMI). The SIMD deprivation category is a postcode measure derived from multiple aspects of deprivation including employment, income, health, education, access to services, crime and housing.

Analysis

In survival analyses, women were followed up from the date of diagnosis of gestational diabetes. Women who had more than one pregnancy during the study period were followed up from the earliest date of diagnosis of gestational diabetes. The relationships between potential risk factors and development of T2D were assessed by univariate and multivariate Cox regression, from which hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Deprivation category, age, history of GDM, family history of diabetes, use of insulin during pregnancy, average weekly weight gain and weight, trimester, HbA1c, FBG, 2 h BG at diagnosis of GDM were entered as independent variables, with diagnosis of T2D as the dependent variable. Statistical analyses were carried out using SPSS for Windows version 21. Ethical approval was obtained from the School of Nursing, Midwifery and Health at the University of Stirling. The Tayside Committee for Medical Research Ethics has granted approval for studies using routinely collected, anonymised health data and this study falls under this approval.

Results

Characteristics of population

Data were extracted from the records for 285 women, of which 164 women met the criteria for GDM and had no previous diagnosis of Type 1 or Type 2 diabetes, and were therefore included in the study. Of the remainder, 75 women had Type 1 Diabetes, 12 had Type 2 Diabetes, 2 were diagnosed with GDM in the first trimester and 1 had maturity onset diabetes of the young. A further 21 women were classified as borderline GDM as their blood

glucose results were high but did not meet the criteria for GDM. Ten women with GDM were excluded due to having missing data or a previous diagnosis of Type 1 or Type 2 diabetes.

At the time of diagnosis of GDM, women ranged in age from 16 to 43 with a mean age of 30. Table 1 shows further characteristics of the population. Women were more commonly from areas of higher deprivation than lower deprivation. A positive family history of diabetes was noted for around a third of women and the majority were having their first or second child. BMI data were not recorded for the majority of women in this study.

Progression to type 2 diabetes

Forty one women (25%) developed T2D during follow-up. The time between diagnosis of GDM and T2D ranged from 4 months to nearly 16 years, with a mean time of 93 months (SD = 48.2) or nearly 8 years. Of these women only 3 (7.3%) went on to develop T2D in the two years after their diagnosis of GDM and a further 4 (9.8%) developed T2D two to four years after their diagnosis of GDM. Figure 1 shows a relatively steady rate of T2D incidence after diagnosis of GDM over the study period. Table 2 shows the results of both univariate and multivariate Cox survival analysis. Greater weight during pregnancy, insulin use during pregnancy, higher HbA1c levels and FBG were associated with highly elevated risks of progression to T2D in univariate and multivariate analyses. Although 2 h BG and were also associated with an increased risk univariately, this association was no longer statistically significant after adjusting for other variables. While there were no statistically significant associations for increasing age, family history of T2D or previous history of GDM, the hazard ratios were elevated. There was no evidence for an association with deprivation or average weekly weight gain.

Table 1 Characteristics of the population

Deprivation category	n (%)
5 (Lowest Deprivation)	17 (10.4)
4	39 (23.8)
3	21 (12.8)
2	35 (21.3)
1 (Highest Deprivation)	44 (26.8)
Data Missing	8 (4.9)
Previous live births	**n (%)**
0	57 (34.8)
1	54 (32.9)
2	28 (17)
3 or more	19 (11.6)
Data Missing	6 (3.7)
Mother's weight (kg)	**n (%)**
Up to 76.8	46 (28)
76.8-92.5	49 (29.9)
Over 92.5	53 (32.3)
Data Missing	16 (9.8)

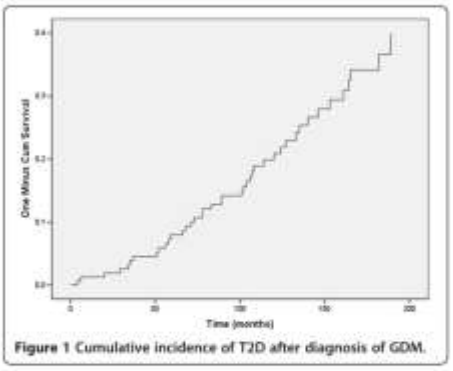

Figure 1 Cumulative incidence of T2D after diagnosis of GDM.

Discussion

To the best of our knowledge this study is the first to investigate progression from GDM to T2D in the UK. We found that around a quarter of women diagnosed with GDM developed T2D with a mean time window between the two diagnoses of 8 years. The vast majority of women who did develop T2D after GDM did so five years or more after their diagnosis of GDM. This time period presents a considerable window of opportunity to deliver an intervention and for women to make necessary changes to their diet and activity levels in order to reduce the risk of progression to T2D. Many people find making lifestyle changes difficult and women who have recently had a baby face additional problems. For example, a lack of time is often cited by women who have had GDM as a barrier to making lifestyle changes [13]. Our findings suggest that the window of opportunity may be large enough for the majority of women to allow an intervention to be delayed until the child is slightly older and less dependent. Such a delay may help to address some of the barriers to lifestyle change faced by women with GDM but this argument becomes complex if women are planning to have more children. This issue is further complicated by the fact some women have already made lifestyle changes during pregnancy in an attempt to manage their GDM. With these women it may be best to intervene sooner after pregnancy to ensure these changes are maintained. The timing of lifestyle interventions for women who have had GDM clearly needs further exploration with women, along with the optimal

Table 2 Hazard ratio of developing T2D in patients with GDM according to previous history of GDM, family history of diabetes, deprivation category; insulin use and average weekly weight gain during pregnancy; and weight, age, trimester, HbA1c, fasting and 2 hour blood glucose at diagnosis of GDM

	Univariate				Multivariate	
	No. (%) progressing to T2D	Mean time to progress (months)	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Whole sample (n=164)	41 (25)	93				
Deprivation category (no. in each group)						
5 least deprived (17)	2 (12)	21	1.00		1.00	
4 (39)	8 (21)	78	1.44 (0.31-6.76)	0.647	0.68 (0.12-3.95)	0.671
3 (21)	6 (29)	94	1.86 (0.38-9.20)	0.448	0.71 (0.11-4.61)	0.717
2 (35)	13 (37)	115	2.81 (0.63-12.45)	0.174	1.92 (0.37-10)	0.438
1 most deprived (44)	11 (25)	82	1.76 (0.39-8.89)	0.461	0.76 (0.15-3.93)	0.742
Data missing (8)	1 (13)	106	0.81 (0.07-8.89)	0.860	0.9 (0.07-11.96)	0.936
Age (no.)						
25 and under (32)	6 (19)	99	1.00		1.00	
26 to 34 (84)	19 (23)	93	1.28 (0.51-3.19)	0.604	1.35(0.48-3.79)	0.570
35 and over (48)	16 (33)	86	1.90 (0.74-4.87)	0.179	2.38 (0.82-6.95)	0.112
Previous history of GDM (no.)						
Yes (11)	4 (36)	83	1.7 (0.61-4.77)	0.315	2.83 (0.62-12.87)	0.179
No/Data missing (153)	37 (24)	91	1.00		1.00	
Family history of diabetes (no.)						
Yes (59)	17 (29)	89	0.80 (0.43-1.49)	0.485	1.42 (0.64-3.15)	0.385
No/Data missing (105)	24 (23)	93	1.00		1.00	
Weight (no.)						
Up to 76.8 kg (46)	3 (7)	70	1.00		1.00	
76.8 to 92.5kg (49)	15 (31)	88	5.19 (1.5-17.93)	0.009	4.98 (1.23-20.18)	0.024
Over 92.5kg (53)	20 (38)	89	6.49 (1.93-21.86)	0.003	5.22 (1.38-19.73)	0.015
Data missing (16)	3 (19)	150	3.05 (0.62-15.12)	0.172	3.5 (0.53-23.34)	0.196
Trimester at diagnosis (no.)						
2nd trimester (16)	5 (31)	96	1.21 (0.47-3.07)	0.696	1.05 (0.32-3.45)	0.942
3rd trimester (147)	36 (24)	90	1.00		1.00	
HbA1c in mmol/mol (no.)						
33.3 and under (19)	3 (16)	150	1.00		1.00	
33.3 to 42.1 (22)	5 (23)	82	1.42 (0.34-5.95)	0.630	1.59 (0.29-8.84)	0.597
42.1 plus (18)	8 (44)	57	4.41 (1.17-16.69)	0.029	5.34 (0.98-29)	0.052
Data missing (105)	25 (24)	98	1.66 (0.5-5.5)	0.407	1.9 (0.45-7.94)	0.381
Fasting blood glucose in mmol/l (no.)						
Under 5.1 (52)	6 (12)	102	1.00		1.00	
5.1 to 7.0 (72)	20 (28)	93	2.62 (1.05-6.53)	0.038	1.66 (0.52-5.24)	0.392
Over 7.0 (17)	6 (35)	60	6.87 (2.2-21.44)	0.001	3.94 (0.92-16.91)	0.065
Data missing (23)	9 (39)	99	3.87 (1.38-10.89)	0.010	35.29 (2.18-570.68)	0.012

Table 2 Hazard ratio of developing T2D in patients with GDM according to previous history of GDM, family history of diabetes, deprivation category; insulin use and average weekly weight gain during pregnancy; and weight, age, trimester, HbA1c, fasting and 2 hour blood glucose at diagnosis of GDM *(Continued)*

2 hour post load blood glucose in mmol/l (no.)						
Under 8.5 (39)	7 (18)	83	1.00		1.00	
8.5-11.1 (67)	14 (21)	96	1.15 (0.46-2.85)	0.762	1.54 (0.54-4.38)	0.417
Over 11.1 (36)	12 (33)	84	2.58 (1.01-6.56)	0.047	2.37 (0.76-7.4)	0.139
Data missing (22)	8 (36)	99	2.13 (0.77-5.88)	0.144	0.1 (0.01-1.56)	0.101
Used Insulin during pregnancy (no.)						
Yes (51)	20 (39)	88	2.82 (1.52-5.2)	0.001	2.81 (1.35-5.86)	0.006
No (113)	21 (19)	94	1.00		1.00	
Average weekly weight gain (kg)						
0.3 and under (61)	16 (26)	82	1.00			
0.31 and above (64)	14 (22)	90	0.71 (0.35-1.47)	0.360	0.61 (0.2-1.45)	0.259
Data Missing (39)	11 (28)	105	1.04 (0.49-2.25)	0.912	1.12 (0.43-2.93)	0.821

content and means of delivery, if interventions are to be successful.

Women who were at highest risk of developing T2D after GDM were heavier women, those with an HbA1c of over 42.1 mg/dL, those who used insulin during their pregnancy and those with FBG of 7.0 mmol/l and over. These women should arguably be prioritised for intervention. These findings are largely consistent with previous research reported in a systematic review of studies assessing the incidence of T2D after a diagnosis of GDM [7].

Higher FBG levels and HbA1c were associated with higher risk univariately, but this increased risk was only marginally significant in the multivariate analysis. However, we identified an increased risk of four fold for women who had an FBG of 7.0 and over five fold for women with an HbA1c of over 42.1 mg/dL. Given the small sample size and wide confidence intervals in this study, these marginally significant risks cannot be discounted. It is difficult to compare our finding for FBG with previous research that has generally looked at FBG as a continuous variable; thus particular thresholds of FBG for increased risk of T2D have been difficult to pinpoint. Studies that did use categories for FBG reported varying findings. One study found an 11 fold risk in women who had an FBG of 5.9 or over compared to those with lower FBG values [14]. Two other studies reported that women who went on to develop T2D had a mean FBG of closer to 8.0 [15,16].

The systematic review of studies assessing the incidence of T2D after a diagnosis of GDM [7] reported mixed findings for the association between BMI and future T2D risk. There were insufficient data for BMI in the present study to include it in the survival analysis. However, weight was found to be significantly associated with increased risk of T2D in the multivariate analysis, with other factors such as trimester controlled for. Although weight is typically regarded as an unreliable measure of obesity and disease risk as it does not take into account height, our study does suggest that it may be a useful indicator of future risk of T2D in women with GDM.

We did not find statistically significant associations between increasing age, history of GDM in a previous pregnancy or family history of diabetes and future risk of T2D. Although the hazard ratio estimates were elevated, particularly for previous history of GDM, and therefore increased risks cannot be discounted, the sample size in our study was relatively small and confidence intervals were wide. Previous research reports mixed results for these risk factors; therefore larger studies are required to verify the results.

Despite being a small study, the diagnosis of GDM in our sample of 164 women was validated for each one and we are confident in the high quality of our data. Detailed information was collected from paper records using a predefined data collection tool. The subsequent T2D diagnoses were made using a diabetes clinical information system that has been extensively used in health care research and is known to be accurate. However, with around 2,600 births per year in Dundee and Angus, it is clear that we did not identify all cases of GDM during the study period. We would have expected to identify between 500 and 600 women over the period of the study using a conservative rate of 2% of pregnancies affected by GDM. On the other hand, we know that the women that we did include definitely had GDM, even if they represent a sample only.

Reasons for the low number of women identified with GDM might include the non-universal screening of women for GDM, 'lost' paper-based records, women attending other diabetes antenatal clinics in the region or women treated solely in primary care or general antenatal clinics. It is also likely that a proportion of women who had GDM went undiagnosed due to lower awareness of the condition in the past. Another limitation of this study was the high level of missing data in the paper records for several of the variables of interest which limited our ability to investigate them in depth. Despite these limitations, this is the first study of its kind to be carried out in the UK. The region in which the study was carried out is broadly representative of the total population of Scotland and the results are more generalizable to the UK than similar studies in Europe and the United States.

Conclusions

In summary, this study clearly shows how a diagnosis of GDM can have an adverse impact on health that extends long after the pregnancy. This study highlights those women with GDM who are at the greatest risk of progressing from GDM to T2D and should therefore be prioritised for preventative intervention and suggests there is a viable time window to prevent progression from GDM to T2D in the majority of women. While a diagnosis of GDM presents an ideal opportunity for an intervention to reduce the growing burden of T2D, identifying the most effective way and optimal time to help women who are at a particularly busy period of their lives to engage in lifestyle change remains a challenge that needs further exploration.

Abbreviations

2 h BG: 2 hour blood glucose; BMI: Body mass index; FBG: Fasting blood glucose; GDM: Gestational diabetes mellitus; HbaIc: Glycated haemoglobin; OGTT: Oral glucose tolerance test; SCI-DC: Scottish care information – diabetes collaboration; SIMD: Scottish Index of multiple deprivation; T2D: Type 2 diabetes; WHO: World Health Organisation; RBG: Random blood glucose.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CE was primarily responsible for gaining access to the data, data extraction, analysis and drafting the manuscript. GL was involved in conceiving the study, acquisition of data and drafting of the manuscript. MS carried out data extraction and drafting of the manuscript. JE was involved in conceiving the study, data analysis and drafting the manuscript. HC participated in drafting and revising the manuscript. All authors read and approved the final manuscript.

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Appendix 10

PDF of published manuscript for publication 5.

DIABETICMedicine

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Research: Pregnancy

Postnatal experiences, knowledge and perceptions of women with gestational diabetes

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Abstract

Aim Women with gestational diabetes mellitus (GDM) are at increased risk of Type 2 diabetes. This study aimed to explore experiences, knowledge and perceptions of women with GDM to inform the design of interventions to prevent or delay Type 2 diabetes.

Methods Semi-structured interviews were carried out with 16 women with GDM who were recruited from a clinic in one Scottish health board. A framework approach was used to manage and analyse data according to themes informed by psychological theory (self-regulation model and theory of planned behaviour).

Results GDM is not seen as an important, or even real diagnosis among some women, and this perception may result from the perceived minimal impact of GDM on their lives. Some women did experience a bigger emotional and practical impact. Knowledge and understanding of Type 2 diabetes was poor in general and many women were unconcerned about their future risk. Lower concern appeared to be linked to a lower perceived impact of GDM. Lifestyle changes discussed by women mostly related to diet and were motivated primarily by concern for their baby's health. Many women did not maintain these changes postnatally, reporting significant barriers.

Conclusions This study has suggested potential avenues to be explored in terms of content, timing and potential recipients of interventions. Educational interventions postnatally could address illness perceptions in women with GDM and redress the situation where lack of aftercare downplays its seriousness. For lifestyle interventions, the child's health could be used as a motivator within the context of later joint or family interventions.

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Introduction

Women with gestational diabetes mellitus (GDM) are at an increased risk of developing Type 2 diabetes. GDM affects around 5% of pregnancies in Europe [1]. In women with GDM, normal glucose regulation usually returns shortly after delivery, but these women have up to a sevenfold increased risk of Type 2 diabetes compared with women who have not had GDM [2]. Lifestyle interventions targeted at high-risk individuals can prevent or delay the onset of Type 2 diabetes [3]. However, the evidence for interventions that specifically target women with prior GDM is not as compelling [4] and many studies report difficulties in recruiting and retaining participants [5]. The challenges facing women with GDM in making lifestyle changes are potentially quite different from those facing other high-risk patient groups (e.g. people with impaired glucose regulation).

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Learning about the experiences of women with GDM may help to identify whether and which common beliefs and perceptions might be a barrier (or facilitator) to behaviour change, and to help ensure that interventions are appropriately tailored to them. This is important because uptake and engagement with such interventions can be compromised if insufficient attention is paid to the values and concerns of the intended recipients.

There has been relatively little research in the UK exploring the perceptions of women with GDM about this condition and their future risk of Type 2 diabetes. Although there has been a meta-synthesis of 16 studies on this topic [6], only one study is UK-based [7]. These studies have shown that some women have an awareness of their increased Type 2 diabetes risk, but lifestyle changes that are made during pregnancy are difficult to maintain in the longer term [7]. Clearer information is needed, and interventions required that are tailored to women as patients, but also as caregivers [6].

What's new?

- This qualitative study exploring the experiences of 16 women with gestational diabetes established that gestational diabetes (GDM) is not seen as an important, or even real, diagnosis among some women.
- This perception may come about because of the perceived minimal impact of GDM on women's lives.
- This perception may be reinforced by a lack of aftercare once GDM resolves post pregnancy.
- Educational interventions are needed to address illness perceptions surrounding GDM, while lifestyle interventions could use the child's health as a motivator for joint or family interventions.

Medical Research Council (MRC) guidance on developing complex interventions suggests that an appropriate theoretical basis should be identified at the earliest stages of intervention development [8]. It is argued that the use of theory in intervention design increases the likelihood that an intervention will be effective by ensuring that the causal determinants of behaviour are understood and addressed [9]. The overall aim of this study was therefore to explore qualitatively the perceptions and experiences of women with GDM in Scotland surrounding their diagnosis, their future risk of Type 2 diabetes and preventative lifestyle behaviour, and to identify implications for the development of potential interventions to reduce subsequent Type 2 diabetes risk.

Methods

Theoretical framework

This study was framed by a theoretical approach that combined both the Self-Regulation Model [10] and the theory of planned behaviour [11]. The Self-Regulation Model focuses on patients' beliefs about their health condition and proposes that people interpret information about a potential illness to create a 'lay' view or representation of the illness. The coping responses then employed (e.g. adhering to treatment regimens or attending appointments), are related to the illness representations the individual holds and to their appraisal of how successful they perceive their chosen coping responses to be. These illness representations are formed around seven different themes: identity (label or diagnosis of illness); cause (factors believed to have caused the illness); timeline (expected duration of illness); consequences (expected effects of illness on physical, social and psychological well-being); control/cure (extent to which illness can be controlled/cured); emotional representations (emotional responses to an illness); and illness coherence (how well the person understands their illness).

The theory of planned behaviour [11] is concerned with beliefs about lifestyle behaviours and asserts that voluntary behaviours are largely predicted by our intentions regarding the behaviour. Intentions, in turn, are determined by our attitude towards the behaviour (our judgement of whether the behaviour is a good thing to do), subjective norms (our judgement of what important others think of the behaviour) and perceived behavioural control (our expectation of how successful we will be in carrying out the behaviour).

These psychological models have been widely used to understand a wide range of health behaviours and because there was no clear evidence to suggest which approach might be most appropriate in the context of the questions posed by our study [12,13], both models were used to underpin our theoretical approach.

Participants and recruitment

Women were recruited from a diabetes antenatal clinic operating in a single health board in Scotland, UK. They were eligible if they were aged 18 years or over, spoke fluent English and had been diagnosed in their current pregnancy with GDM according to the Scottish Intercollegiate Guidelines Network guidance [14]. Clinical staff identified eligible 49 women from hospital records, gave them information about the study at the clinic and then asked if they were willing for the researcher (CE) to receive their contact details; all women agreed. A convenience sampling approach was used [15]. Interested women either gave their details directly to CE (if she was present) or details were given to CE via clinical staff. The women then received an information sheet about the study and informed that they would potentially be contacted from 8 weeks after delivery. The plan was to conduct approximately 20 interviews, so not all women would be interviewed, and CE collected more names than necessary to allow for drop out. During a post-delivery telephone call, CE checked if the woman was still willing to participate, then scheduled an interview. She had therefore either met or spoken by telephone to every participant before data collection. The final sample size was determined by data saturation, whereby CE conducted interviews until it was felt that no new ideas were being offered by participants.

Data collection

Attempts were made to contact 31 of 49 women post-delivery; women were selected to achieve maximum variation in factors such as age, parity, ethnicity and BMI. Thirteen women could not be reached using the telephone number held by the researcher and two stated they no longer wished to take part. The remaining 16 women were interviewed between January 2015 and August 2017 (Table 1). All interviews were conducted within a year of the women's due date; the majority (14) between 12 and 26 weeks afterwards. Interviews took place in participants'

Table 1 Participant characteristics

Characteristic	N
Age	
20–29	3
30–39	11
> 40	2
Parity	
=1	9
=2	5
=3	2
Gestation at diagnosis of GDM	
First trimester	2
Second trimester	5
Third trimester	8
SIMD deprivation category	
1 (most deprived)	2
2	2
3	5
4	3
5 (least deprived)	4
Ethnicity	
White	12
Asian	3
Black African	1
Participants quoted in text	
P1	Age 39, not first child, white, middle deprivation
P2	Age 42, first child, white, low deprivation
P3	Age 39, not first child, white, high deprivation
P4	Age 22, first child, white, high deprivation
P5	Age 34, first child, not white, high deprivation
P6	Age 35, not first child, white, middle deprivation
P7	Age 35, not first child, white, low deprivation
P8	Age 28, first child, white, low deprivation
P9	Age 38, first child, not white, low deprivation
P10	Age 33, not first child, not white, middle deprivation
P12	Age 38, first child, White, low deprivation
P13	Age 45, first child, white, low deprivation
P14	Age 32, first child, White, middle deprivation
P15	Age 38, first child, not White, low deprivation
P16	Age 25, not first child, white, middle deprivation

GDM, gestational diabetes mellitus.

homes and were carried out by CE (then a part-time PhD student and a registered health psychologist) with previous experience of qualitative fieldwork. The only other individuals present were the baby, or occasionally other children. Participants knew that CE was conducting the study as part of her research degree and that she was not a member of clinical staff but was simply interested in finding out their thoughts on the topic. They were also told that there were no right or wrong answers.

The semi-structured format following an interview guide informed by underlying theory, ensured that the topics of interest were covered while allowing interviewees the freedom to discuss any issues not covered in the guide. The main topics covered were: experiences of diagnosis of GDM, feelings about GDM diagnosis, consequences of GDM, understanding of GDM and information given by healthcare staff, and understanding of Type 2 diabetes and information given by healthcare staff. Only if it was clear that the participant was already aware of increased risk of Type 2 diabetes, were the following topics also discussed: understanding of Type 2 diabetes prevention, lifestyle changes for Type 2 diabetes prevention, advantages and disadvantages of making lifestyle changes for Type 2 diabetes prevention, and views on receiving support to make lifestyle changes after having GDM.

Interviews were audio-recorded with the participant's permission and transcribed verbatim by a professional transcription service (but not returned to the participants). Interviews lasted between 11 and 66 minutes, and field notes written up afterwards. Written informed consent was obtained from all participants and approval to conduct the study was obtained from a National Health Service (NHS) Research Ethics Committee.

Data analysis

Fieldwork and analysis were conducted in parallel rather than sequentially. The framework method [16] was used to organize and analyse the data combined with coding in NVivo 11 qualitative data analysis software. The framework method is relatively structured and allows pre-set objectives and reasoning to inform data collection while still allowing original contributions from participants. The approach involves researchers familiarizing themselves with the interview transcripts, then re-reading them and paraphrasing or labelling any passages they interpret as important. These labels can come from predefined theories or models or can be 'open', that is where anything that is relevant from any perspective is labelled. In this study, the three authors independently reviewed three transcripts and identified and coded areas of interest using an open approach. This open approach was used for the first few transcripts to ensure that any concepts or themes deriving from the data (as well as from theory) were identified.

The three authors then compared their open coding of the three transcripts and agreed that most of the codes could be organized under subthemes derived from the theoretical concepts of the self-regulation model [10] and the theory of planned behaviour [11]. Subthemes were organized under topic themes including GDM, Type 2 diabetes, diet, exercise and reactions to a proposed future GDM intervention. Subthemes included identity, cause, timeline, consequences and control (for data about GDM and Type 2 diabetes). Additional data-derived subthemes

Table 2 Framework used to organize data

Theme	Subtheme (theory subtheme relates to)
1. Background	1.1 Family history*
	1.2 Pregnancy experience*
	1.3 Previous GDM*
	1.4 Postnatal testing*
2. Gestational diabetes mellitus	2.1 Identity (SRM†)
	2.2 Timeline (SRM)
	2.3 Cause (SRM)
	2.4 Consequences (SRM)
	2.5 Control (SRM)
	2.6 Emotional representations (SRM)
	2.7 Illness coherence (SRM)
	2.8 Education about gestational diabetes*
3. Type 2 Diabetes	3.1 Identity (SRM)
	3.2 Timeline (SRM)
	3.3 Cause (SRM)
	3.4 Consequences (SRM)
	3.5 Control (SRM)
	3.6 Emotional representations (SRM)
	3.7 Illness coherence (SRM)
	3.8 Risk perceptions*
	3.9 Prevention*
4. Diet	4.1 Attitude (TPB‡)
	4.2 Subjective norm (TPB)
	4.3 Perceived behavioural control (TPB)
	4.4 Intention (TPB)
	4.5 Behaviour (TPB)
5. Exercise	5.1 Attitude (TPB)
	5.2 Subjective norm (TPB)
	5.3 Perceived behavioural control (TPB)
	5.4 Intention (TPB)
	5.5 Behaviour (TPB)
6. Intervention	6.1 Acceptability*
	6.2 Ideas*

GDM, gestational diabetes mellitus.
*Data-derived subthemes.
†SRM denotes that subtheme taken directly from illness representations of the self-regulation model.
‡TPB denotes that subtheme taken directly taken from/mapped to concepts of the theory of planned behaviour.

included education about GDM and risk perceptions related to Type 2 diabetes. The full list of themes and subthemes are shown in Table 2.

CE then applied the analytical framework to the remaining transcripts and data were summarized using matrices [17]. Six separate matrices were created, one for each topic theme. Each column was labelled with a subtheme (except the first column which contained a participant identifier and demographic data). Each row represented one participant. In each cell of the matrix, relevant data were summarized, and a supporting quote given (a matrix excerpt is shown in Table A1). A further summary matrix was used to juxtapose each summary of the participants' understanding, and perceived impacts, of GDM and Type 2 diabetes. Abstraction and interpretation followed; the matrices were read repeatedly to identify common patterns and disconfirming cases using constant comparison. The findings are presented below as overarching key themes (as depicted in Fig. 1).

Results

The results are discussed under the following overarching themes (mapping to key themes two to six): understanding of GDM, impact of GDM, understanding of Type 2 diabetes and future risk, lifestyle change during and after pregnancy, and prevention of Type 2 diabetes. Verbatim quotes from study participants are identified by participant number. Their characteristics are given in Table 1.

Understanding of GDM

Most women felt they had a good understanding of GDM during their pregnancy. With the time that had elapsed since being diagnosed they struggled to recall specific information about the condition, but most held an overall impression that the information they were given by NHS staff was clear and at an appropriate level. Many praised the staff involved in their care.

> Erm, and they were very good, [the health board] were really, really good. I mean it was, it was about an hour and a half, two hours with the diabetic nurse and she went through everything of . . . and how to use the machine and everything as well. (P9)

When women were less satisfied with the information that they were given, it was generally because this was too vague and not tailored to their specific circumstances, producing feelings of frustration.

> Really to, obviously to eat healthily and exercise but I think the problem is it's very vague as to what eating healthily is. (P7)

> Nobody actually sat down with me and tell me, here's the list of all the food. They gave me a couple of leaflets, erm, but you know, the leaflets is for, erm, you need to customize them based on the patient, what type of food they're used. Because if you're, if you keep telling them, oh don't take, don't have a takeaway, well, I don't have a takeaway, I've already been having healthy eating. (P15)

Although most women explicitly stated that they felt they understood GDM, further discussion revealed areas of confusion or misconception. One was related to the diagnosis of GDM, with some women questioning whether they ever really had the condition. Some suspected that high blood glucose readings identified during diagnostic testing were caused solely by food they had eaten recently, and others felt that a diagnosis very late in pregnancy or one that was

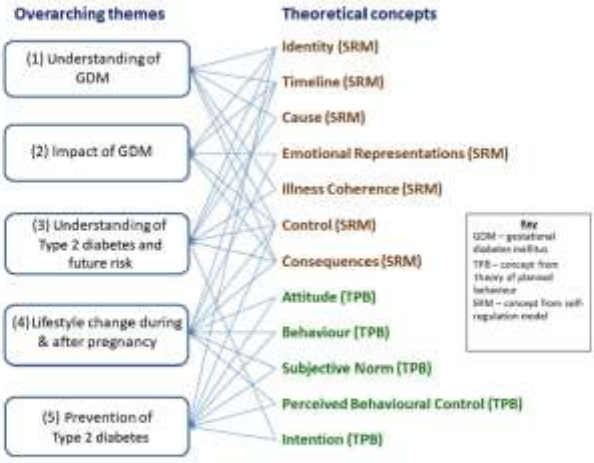

FIGURE 1 Which theoretical concepts informed overarching themes?

classed as borderline meant that the diagnosis was less relevant to them.

> I actually had a big bar of chocolate the day before I went, so I was thinking I bet it's just cause of that. (P8)

> Most of what they were telling you wasn't going to really apply to me because I only had, erm, a couple of weeks to go before, erm, I reached my term time. (P6)

These women often rationalized that since they met the diagnostic criteria for GDM they must have had GDM, but still found themselves questioning the diagnosis.

> So, in one sense you kind of think to yourself, maybe I didnae have it all, and it was just . . . well obviously I did because I had the fasting thing beforehand. (P1)

Although not explicitly stated by participants, this questioning of the diagnosis was possibly linked to their perception that GDM had little impact on their lives; many women who questioned their diagnosis did not experience any symptoms, found GDM easy to control through diet, and had blood glucose readings in the normal range during pregnancy and when tested postnatally.

Other common misconceptions related to the causes of GDM. Although some women correctly identified being overweight, family history of Type 2 diabetes and ethnicity as risk factors for developing GDM, eating sweet and sugary foods was more commonly understood to have been the cause of this condition.

> I was a sugar person first, yeah, yeah, I liked sugar very much . . . I said to the person, maybe because I eat sugar too much. (P10).

Impact of GDM

Perceptions of how much GDM impacted upon participants' lives varied. We identified three groups of women: those for whom the diagnosis had little emotional impact; those for whom the impact was related to concerns about the well-being of their unborn baby; and those for whom the negative emotional impact appeared to last beyond pregnancy. However, the three groups are not necessarily exhaustive or mutually exclusive; this is an emergent finding that needs to be verified.

Women in the first group reported that they were not worried or concerned by the condition at all, with this lack of concern often related to the fact that the condition was relatively common and had little impact on their day to day life.

> It was quite common, so . . . that sort of puts your mind at ease, it didn't scare me or anything. So, it was okay. Knowing that lots of people get it and it was quite normal. . . . (P2)

> But if you manage it quite well it's nothing for you, it's like a part of brushing teeth every day, it's like that. You don't even feel like bad that you've got that gestational diabetes; I never felt bad. (P5).

These women explained that the only real consequence of their diagnosis was having to make changes to their diet, which were viewed as being easy to make, and simply involving cutting out or cutting down sugary foods and drinks; the condition was something temporary that they could forget about after they gave birth.

> No, it's just like a, erm, like buying maternity clothes, and gestational diabetes is like that, and you just forget everything. (P5).

A second group of women had a strong emotional response to being diagnosed with GDM. This was usually caused by worry and guilt that they might have put their unborn baby's health at risk.

> I did, I felt . . . I actually had a wee cry. I was like, oh, I just felt like I'd let myself down and . . . maybe I just pigged out [over ate] too much. Um, and just felt as if I'd let her down. (P8)

Often this concern eased after the initial diagnosis as the women learned more about the condition and found that they were able to control and manage it.

> Um, no, to be honest with you, when, when, when I kept checking my sugar levels and that, I just, kind of, thought, well, cannae be that much of a big thing because I'm, I'm not over and I'm not under. (P8)

Less commonly, concern and emotion about being diagnosed with GDM did not lessen over time, and women in the third group reflected that they were still affected by their diagnosis now. These women had often had a much more difficult time in controlling the condition, requiring dietary control to be supplemented with insulin and medication (something which many women stated being reluctant to do). They reported it as time consuming, they found injecting unpleasant and they suffered side effects from the medication.

> So, um, I ended up having to take insulin, which was horrible as well . . . because they're a needle again. So then I'm testing myself three times a day and my insulin at night, oh, it was just horrible. (P16)

Understanding of Type 2 diabetes and future risk

General understanding of Type 2 diabetes was very poor. A lack of understanding around types of diabetes and the differences between them was widespread, with many women unable to name Type 2 diabetes, and knowing little about it. Some women did identify poor diet and being overweight as risk factors for Type 2 diabetes and knew that it is controlled through diet and/or medication; but very few mentioned the health consequences of Type 2 diabetes and those who did were very vague about these.

> And obviously there's other health stuff as well at the back of it. (P1)

There were some misconceptions over the causes of Type 2 diabetes and its severity. Some women who had older relatives with Type 2 diabetes believed it was a consequence of older age; others downplayed its seriousness, especially when they held a preconception that Type 2 diabetes had little impact.

> So, it's only type two so it's . . . I suppose, it's not as bad but . . . (P4)

> Erm, but my partner's mum she's got Type 2 diabetes and I know that she takes a tablet. I'm sure it's in the morning. And that does her throughout the day. (P4)

Nearly all women recalled being told that they were at an increased risk of diabetes in the future as a result of having had GDM (although few understood the time frame), and that they could reduce their risk through changes to their diet and physical activity levels.

> Maybe not this early and this quick after having them . . . but probably more than likely later on in life, like maybe when I'm 50, 60, they said that I'll probably, I'll probably be likely to have it, yeah. (P16)

However, many women downplayed the risk for themselves, indicating that because they were not overweight or had no other health problems, or because they had a late diagnosis during pregnancy, this meant that their risk was lower than for other women.

> I have to go every year now for blood tests because of it and I do think it's pretty pointless to be perfectly honest because I think if it hadn't been diagnosed, then they would never have been none the wiser. I don't think it's something that I need to worry about in the future to be honest. (P6)

> She has taken my three-day result, or something, and she took my blood as well on that day, and she counted. And she said . . . you're not that much, er, risk of getting Type 2 diabetes. So I thought, okay, that's fine. (P5).

The extent to which women felt concerned by their increased risk of Type 2 diabetes varied, but overall concern was not high. Many women made no mention of being worried about their risk of Type 2 diabetes and one group of women felt that any risk was far in the future.

> It's not an immediate thing for me, I'm not that fussed about it just now. (P9)

However, one participant had a difficult time managing her GDM when pregnant and felt that it had quite a big impact on her day to day life, as did another participant who reported being concerned about her future risk of Type 2 diabetes. This suggests that concern about future risk of Type 2 diabetes may be linked to more severe perceived or actual impact of GDM.

> I really would hate to be . . . to get diabetes again. It's horrible. (P3)

Lifestyle change during and after pregnancy

Lifestyle changes discussed in the interviews predominantly related to changes to diet rather than physical activity. Women commonly described cutting out sweet foods, fizzy drinks and other junk food in response to their GDM diagnosis, after initially having been 'eating for two'.

> I say, for me it was just cutting back on eating cakes and chocolates, which is what I'd been having … being pregnant. (P7)

The dietary changes that women made after a GDM diagnosis were most commonly motivated by their concern for the health of their unborn baby, and by a desire to avoid taking medication to manage their GDM.

> Just thought of the baby and … obviously I didn't want her to be in any danger when she was, when I was having her or anything like that, any complications or anything like that, so it had to be done. (P8)

> Changed my diet just to, kind of, make sure that … because I didn't … I really didn't want to have any, kind of, medication whether it was tablet or, eh, like injection. (P4)

A few women did manage to continue with these changes postnatally, and were currently attending commercial weight loss groups, but most had not managed to maintain the changes. Once the above motivations had passed, looking after their own health postnatally was not a priority for some women, especially in the face of many new challenges.

> No, but you, you just need to find some energy sometimes. And eating seems to be the right plan for that, but it never is. You just, you know, the sleep deprivation, and, erm, the constant, kind of, needing to be someone else's … you don't really look after yourself so much. (P13)

Changes to physical activity levels were less commonly discussed by participants in this study. Some women recalled being advised to increase their activity levels when they were diagnosed (although this advice was briefer and more peripheral to the education they received on diet), whereas others did not receive any such advice. There was therefore confusion over what was appropriate.

> I mean exercise, like I said, do more exercise. Walking, jogging, it … what kind of, you know, what, what would prevent it? So no, they didn't really … It was just like do some more exercise and stuff, yeah. (P9)

Among those who did increase physical activity levels, walking, then swimming, were the activities most frequently mentioned. Some women who had previously been active managed to continue this activity during their pregnancy, although others reported that they reduced or stopped this exercise during pregnancy. Barriers included having a bump and feeling heavily pregnant, pregnancy-related back and pelvic pain, the demands of having one or more children to look after, tiredness and poor weather.

> Where exactly am I meant to go and how am I meant to do this, when I can't nip out to the gym, I can't go and walk the dog, or I can't nip out and see a friend 'cause she's in bed. (P1)

Prevention of Type 2 diabetes

The majority of women stated that they would be open to additional support to make lifestyle changes after giving birth. However, two women stated clearly that they would not be interested, while another felt that there was already support available. Among those women who welcomed the idea there was a feeling of being left on their own after the high level of care they had received when they had GDM.

> Um, yeah, I would have … probably … looking back on it now, um, I'd have maybe liked a wee bit more, like, sort of, closure on it, a wee bit more explanation. (P12)

Although some women were invited to attend postnatal testing to ensure that their blood sugar levels had returned to normal, others reported that they had to arrange this testing themselves. This lack of aftercare led some women to question how serious their increased risk of Type 2 diabetes was.

> But because there's nothing … no after care as such … then you know, it's not like a major thing. (P9)

These women felt that a greater level of aftercare might help to increase their motivation to make lifestyle changes to reduce their Type 2 diabetes risk. Some suggested that additional blood testing over the longer term would be beneficial. One woman who was awaiting the results of her postnatal testing described how going for this test had made her think more consciously about her lifestyle.

> When I had the letter through for to say for to go, em, for to get tested, and then you start to think, aah, oh wait a wee minute … and then have I really been paying attention or have I not … I know this sounds terrible, but in one sense I'm hoping it comes back quite high to give myself sort of a kick in the bum, do you know what I mean. (P1)

As previously discussed, some women felt a need for more specific information about making changes to their lifestyle and suggested that this could be tied in with going for postnatal blood testing. Other women felt that group support to make lifestyle changes that involved other mums would be most beneficial for them.

> As much as I love my mum, not just your mum going … you're doing well and you've lost a wee bit of weight, well

done and it took me so long after I'd had babies and stuff, but girls that are going through it . . . that are exactly the same as you. And that's been a really good support network. . .. (P2)

Women who lived outside the main towns/cities in the health board also noted that there were fewer group activities available to them.

Discussion

This study provides an understanding of women's perceptions and experiences of GDM, of making lifestyle changes after a diagnosis of GDM and their risk perceptions about Type 2 diabetes. In general, most women in this Scottish study had a positive experience of health care after their GDM diagnosis, as reported elsewhere in the UK [7], but in contrast to the findings from a synthesis of international qualitative studies [6]. However, women identified an explicit need for more specific dietary advice, and advice on physical activity, during pregnancy and in the postnatal period.

While the transitory nature of GDM was emphasized by some women in this, and other studies [6], the belief that GDM is not an important (or even real) diagnosis, has not been explored previously, and often occurred among women for whom the perceived impact of GDM was minimal. Similarly, although most women had some (often vague) awareness of their future Type 2 diabetes risk (confirming previous studies [6,7]), a lack of concern again appeared to tie in with a minimal perceived impact of GDM. This is an important group of women to identify and target for preventative intervention, so that they understand the importance of behaviour change even if their GDM diagnosis did not seem significant at the time.

The perception among some women that GDM was an insignificant diagnosis without longer-term implications, was reinforced by the perceived lack of after care and follow-up. If such follow-up were provided, this might act to counter the postnatal resolution of GDM 'lulling women into complacency' [7].

Many women did achieve dietary and/or exercise behaviour change during pregnancy, and this was often motivated primarily by concern for their baby's health. This ties in with the worry and guilt that increased the emotional impact of GDM among some women. However, awareness of Type 2 diabetes risk did not provide sufficient motivation to overcome barriers to lifestyle change postnatally (including tiredness, lack of energy and the demands of a new baby).

The strengths of this study include the participation of women with a range of different demographic characteristics such as age, ethnicity and deprivation. By using theoretical models to inform the design and analysis, we have highlighted a range of beliefs and illness perceptions that impact upon lifestyle change both during and after pregnancy. The sample size was relatively small, and all women were recruited from one health board; this may mean that the experiences of care that women reported may not be comparable to women in other geographical areas. It was also only possible to ask questions about women's views surrounding Type 2 diabetes once they had indicated that they were already aware of their increased Type 2 diabetes risk. Although this may have introduced a slight bias, it was a requirement stipulated for ethical reasons, in order that women were not distressed by their sudden realization of longer-term and more serious consequences of GDM. While we ensured that a selection of transcripts was coded independently by all three authors and the framework was developed through discussion between them to allow for varied and richer interpretations of the data, it is still possible that this study was influenced by the researchers' backgrounds and beliefs. Despite these limitations, our findings accord and build upon those from a previous UK study [7].

Findings for this study have important implications for the development of potential interventions for women who have had GDM. Regarding educational interventions, given the perception of GDM as being short-lived, easily controlled and having few consequences, this study suggests that illness perceptions surrounding GDM (as defined in the self-regulation model), particularly the 'consequences', need to be addressed; and would be appropriately aimed at women for whom the perceived impact of GDM was minimal. The 'timeline' and 'consequences' of Type 2 diabetes are also poorly understood and could be tackled. Timing such an educational intervention soon after delivery, combined with longer-term follow-up and testing, would help to redress the situation where a current lack of aftercare downplays the seriousness of GDM and subsequent Type 2 diabetes risk.

In terms of lifestyle interventions for behaviour change, it is clear that women feel the need for more specific dietary and physical activity advice. There are significant barriers to behaviour change with a young family (perceived behavioural control in the theory of planned behaviour). However, given that the health of their unborn baby facilitates behaviour change during pregnancy, it may be that an important later source of motivation could be their child's health, which could be used to target behavioural attitudes and intentions within the context of a joint or family intervention. Although other studies have identified weaning as a time of increased receptiveness to lifestyle change [6], this logic could extend to other times during a child's development.

In summary, this qualitative research with women about their experiences of GDM, underpinned by psychological theory, has suggested potential avenues to be explored further in terms of content, timing and potential recipients of interventions to reduce the risk of Type 2 diabetes in women who have had GDM.

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Competing interests

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. How the theoretical concepts informed over-arching themes.

Appendix 1

Table A1 Illustrative excerpt from an analytical framework matrix for GDM topic theme

2. GDM	2.1 Identity	2.2 Timeline	2.3 Cause	2.4 Emotional representations	2.5 Consequences	2.6 Control	2.7 Illness coherence	2.8 GDM education	Theme summary
Patient 1 Age: late 30s Baby age: 3 months Parity: +2 Dep: Middle (3)	Felt very tired but questioned whether the high blood glucose readings were down to eating a lot. '... maybe I didnae have it all, and it was just ... well obviously I did'	Viewed as temporary. 'I don't need to remember that now because I've had her ... and she tested fine'	Caused by diet. 'I'd already set myself down the road to the gestation diabetes ... because I was stuffing Mars Bars in my mouth like you wouldnae believe [laugh] for to try and get a bit of energy about me'	Saw diagnosis as a wake-up call, but not overly concerned. Mostly concerned about baby rather than herself. 'it doesn't really matter about me.'	Talked about the consequences for her baby and for delivery. 'you see these babies that just look so puffy and ... not ill, because they don't look ill, but just sort of ... oh my god, what a shame, and I've done that to you, kind of thing. And then step two pops in and you think, how am I gonna to get that out? [Both laugh]. It it's like a twelve pound baby because it's all swollen in'	Felt it was easy to control with diet. 'they gave me the wee kit for to like, for to test the blood and things. And because you could see it was working, what you were doing'	No data	Didn't remember much but felt she it was fine at the time. 'It was fine. It wasnae like it was information overload or too technical or anything like that. It was alright, it was alright.'	Questioned diagnosis and thought it was caused by her diet. Concerned for baby rather than herself. Doesn't seem to have had big impact on her life and found it easy to control. Viewed as temporary.
Patient 2 Age: early 40s Baby age: 3 months Parity: +1 Dep: Low (4)	Had read about it in books about pregnancy. Felt tired. 'I felt that at night time I was getting really tired ... and I knew that if I fell asleep early I wouldn't sleep at night'	N/D	Caused by diet, particularly chocolate eaten to give her energy when she was tired. 'I don't normally eat chocolate and I think that might have triggered ... the diabetes' Besides eating chocolate she felt she was very healthy and so was confused about why she got it and suggests it's just 'one of those things'.	Not scared as saw it as something quite common. 'it was quite common, so ... that sort of puts your mind at ease, it didn't scare me or anything. So, it was okay. Knowing that lots of people get it and it was quite normal, and the people at the hospital were really nice ... and they spoke you through everything that happens ... and it was fine.'	Mentioned the risk of getting GDM again in future.	Found it easy to get under control through diet, particularly cutting out chocolate. 'it was quite easy to get under control ... it really was, just, as I said, cutting out the chocolate at night'	No data	Staff at hospital were nice and didn't make too big a thing about it. Felt she already knew a lot of what they were telling her about diet, 'and then at the hospital they were really, really nice ... and they didn't make it a big thing ...	Thought it was caused by diet. Found it easy to control and saw it as something quite common so wasn't concerned.

Table A1 *(Continued)*

2. GDM	2.1 Identity	2.2 Timeline	2.3 Cause	2.4 Emotional representations	2.5 Consequences	2.6 Control	2.7 Illness coherence	2.8 GDM education	Theme summary
								which you don't need when you're pregnant.'	
Patient 4 Age: early 20s Baby age: 6 months Parity: +1 Dep. High (1)	Was thirsty and going to the toilet more. 'Erm, I didn't actually know that you could get diabetes when you were pregnant.'	Viewed as temporary: 'So, it was only for so long and then they're here.'	Caused by diet. 'I had been really quite bad with my food to the extent it led me to get, eh, the gestational diabetes.'	Wasn't too bothered but partner was worried and upset. 'Erm, and ... but it didn't really bother me because my wee sister's got diabetes and so has my partner.' 'My partner was quite, erm .... he was quite upset'	Didn't discuss apart from saying partner worried about the chance of the baby having diabetes. 'he was saying he didn't want him to have diabetes when he was born and things like that'	Bloods were pretty normal through watching her diet. 'I think, that was probably why my blood was always a lot better. Eh, and why it was never over just because I had changed from just eating sweeties and crisps and basically whatever I wanted to being a bit healthier as my diet again'	Wasn't something she knew about before pregnancy. 'Erm, I didn't actually know that you could get diabetes when you were pregnant. Eh, I didn't know that was a thing, erm, but it was fine'	Felt it was explained well and wasn't too complicated.	Thought it was caused by her diet. Not worried and managed to control through diet. Viewed as temporary.

Appendix 11

School of Nursing, Midwifery and Health Research Ethics Committee approval letter for publication 5.

CMR/SG

13 November 2013

Claire Eades
Clinical Academic Fellow
School of Nursing, Midwifery and Health
University of Stirling
Stirling
FK9 4LA

UNIVERSITY OF STIRLING

SCHOOL OF
NURSING, MIDWIFERY
AND HEALTH

Email: nursingmidwifery@stir.ac.uk
Web: www.nm.stir.ac.uk

Michelle Roxburgh
Committee member
School Research Ethics Committee

School of Nursing, Midwifery and Health
University of Stirling
Stirling FK9 4LA

Tel: +44 (0) 1463 255624
Fax: +44 (0) 1786 466333
Email: cmr3@stir.ac.uk

Dear Claire

Exploring postnatal experiences, knowledge and perceptions of women with gestational diabetes

Thank you for submitting your ethics application for a study titled: Exploring postnatal experiences, knowledge and perceptions of women with gestational diabetes.

The School of Nursing, Midwifery and Health Ethics Committee reviewed your application today and we are pleased to advise you that approval has been given for this study.

The Committee were impressed with the level of detail and thought put into this application and had no concerns on ethical grounds.

Prior to submitting your application to IRAS the committee recommends one very minor amendment under section A17-2 – Exclusion criteria to point 4 – 'Women who have had serious complications during their pregnancy or birth'. We would suggest that in the bracketed section that you put in with words to the effect 'physical or psychological complications'.

Thank you again for submitting this proposal and congratulations.

May I take this opportunity to remind you that a site-file of *all* documents related to the research should be maintained throughout the life of the project, and kept up to date at all times. The site file template can be found on the SREC page of the School's website. Please bear in mind that your study could be audited for adherence to research governance and research ethics protocols.

Yours sincerely

Michelle Roxburgh
(Committee member)
School of Nursing, Midwifery and Health Research Ethics Committee

Appendix 12

NHS East of Scotland Research Ethics Committee approval letter for publication 5.

EoSRES

NHS SCOTLAND
Research Ethics Service

East of Scotland Research Ethics Service (EoSRES) REC 1
Tayside Medical Sciences Centre (TASC)
Residency Block C, Level 3
Ninewells Hospital & Medical School
George Pirie Way
Dundee DD1 9SY

Miss Claire Eades
Clinical Academic Fellow
School of Nursing, Midwifery and Health
RG Bomont Building
University of Stirling
FK9 4LA

Date: 6 February 2014
Your Ref:
Our Ref: AG/14/ES/0003
Enquiries to: Mrs Arlene Grubb
Extension: Ninewells extension: 2283848
Direct Line: 01382 383848
Email: Eosres.tayside@nhs.net

Dear Miss Eades

Study title: **Exploring postnatal experiences, knowledge and perceptions of women with gestational diabetes.**
REC reference: **14/ES/0003**
Protocol number: **n/a**
IRAS project ID: **141750**

Thank you for your letter of 04 February 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Mrs Arlene Grubb, agrubb@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering Letter		11 December 2013
Evidence of insurance or indemnity		29 November 2013
Interview Schedules/Topic Guides	2	29 October 2013
Investigator CV: Eades		
Investigator CV: Evans		
Letter from Sponsor		29 November 2013
Other: Letter from Funder		21 November 2013
Participant Consent Form: Tracked Changes	2	04 February 2014
Participant Information Sheet: Tracked Changes	2	04 February 2014

Protocol	2	29 October 2013
REC application		11 December 2013
Response to Request for Further Information		04 February 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

14/ES/0003 **Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

Arlene Grubb *for*
Dr Carol Macmillan
Chair
Email: **Eosres.tayside@nhs.net**

Enclosures: "After ethical review – guidance for researchers" [SL-AR2]

Copy to: Heather Allen
Ms Allyson Bailey, NHS Forth Valley Research and Development Office

Appendix 13

NHS Tayside research and development approval letter for publication 5.

NHS
Forth Valley

Research and Development Office
Administration Offices
Falkirk Community Hospital
Westburn Avenue
Falkirk FK1 5SU
Tel 01324 677564
Date: 07 April 2014

PRIVATE & CONFIDENTIAL

Miss Claire Eades
Clinical Academic Fellow
School of Nursing, Midwifery and Health
RG Bomont Building
University of Stirling
FK9 4LA

Dear Miss Eades

Letter of Access : Exploring Postnatal experiences, knowledge and perceptions of women with gestational diabetes 14/ES/0003

This letter confirms your right of access to conduct research through NHS Forth Valley for the purpose and on the terms and conditions set out below. This right of access commences **when you return a signed copy of this Letter** and ends on **01 February 2015** unless terminated earlier in accordance with the clauses below

DETAILS OF ACCESS

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Chief Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at NHS Forth Valley has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out. If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Your activities in NHS Forth Valley under this agreement will be **providing further information about the study and obtaining contact details from patients who express an interest in taking part in the study and consenting participants**. Your named contacts for the duration of the study will be **Linda Buchanan, clinical contact** and **Rosemary Wilson, R&D officer.**

CONDUCT

You must carry out your duties under this contract in accordance with policies, practices and procedures established by the Board and varied from time to time. NHS Forth Valley Board manages all research in accordance with the requirements of the Scottish Executive Research

Governance Framework for Health and Community Care. While carrying out research within NHS Forth Valley you must comply with all reporting requirements, systems and duties of action put in place by the Board to deliver research governance where this is relevant to your work with the Board. You are also required to comply with all laws and statutes applicable to the performance of the study including, but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Medicines Act 1968, the Medicines for Human Use (Clinical Trial) Regulations 2004, and with all relevant guidance relating to medicines and clinical trials from time to time in force including, but not limited to, the ICH GCP and the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version). You are required to co-operate with NHS Forth Valley in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on NHS Forth Valley premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution. In the course of your duties you may have access to information about staff or patients or other aspects of the Board's activities, about which you have a duty to maintain confidentiality at all times. In common with all other staff you have, in addition, a responsibility to ensure that information relating to your work and the operation of the Board in general is kept and maintained securely and you are obliged to receive, store and dispose of data in accordance with Board policies and good practice. In particular, the disclosure of commercial or other confidential information which may affect the Board's business interests or endangers the survival of any of its services will be regarded as a fundamental breach of the mutual confidence which must exist between the Board and yourself. You should seek advice from the Medical Director or the Board's Data Protection Officer if you are in any doubt whatsoever. Unauthorised disclosure or removal of information may lead to consideration of termination of the honorary appointment. You are further obligated under this agreement to report to your R&D Office contact person any infringements either by accident or otherwise which constitute a breach of confidentiality. The R&D Office contact person will then be responsible for notifying the data-protection officer for NHS Forth Valley.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property, with the exception of property handed over and accepted on behalf of the Board for safe custody. You are therefore advised to cover yourself against any such risk by taking out appropriate insurance.

The Board operates a "Tobacco Policy". Smoking is not permitted anywhere within Board premises, grounds or Board vehicles. Failure to comply with this policy will be considered a disciplinary matter.

While undertaking research through NHS Forth Valley you will remain accountable to your employer **University of Stirling** but you are required to follow the reasonable instructions of **Head of relevant NHS Department** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

LEGAL POSITION AND INDEMNITY

You are considered to be a legal visitor to NHS Forth Valley premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee. This agreement does not affect the terms and conditions of any other employment you may currently hold with another employer, who will remain responsible for you and for any disciplinary matters that may arise.

Your substantive employer will remain liable for your acts or omissions in the course of the research project covered by this letter, and must ensure they maintain appropriate indemnity insurance for this purpose. Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Where required by law, your employer will initiate your Independent Safeguarding Authority (ISA) registration, and thereafter, will continue to monitor your ISA registration status via the on-line ISA service. Should you cease to be ISA-registered, this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity. You MUST stop undertaking any regulated activity.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

NHS Forth Valley will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If you agree to accept this agreement on the terms indicated above, please sign the statement of acceptance and return one copy contract to me at the address overleaf, retaining the other for your own reference. A further copy has been sent to **your academic supervisor** for your records.

Yours sincerely

Rosemary Wilson
Research and Development Officer
cc: HR department of the substantive employer

Extension to NHS Forth Valley research and development letter of approval.

NHS Forth Valley

Carseview House
Castle Business Park
Stirling
FK9 4SW

NHS Forth Valley

Research and Development Office
Acute Division Headquarters
Westburn Avenue
Falkirk FK1 5SU
Tel 01324 677564
Email: FV-UHB.RandD-depart@nhs.net
23 November 2016

PRIVATE & CONFIDENTIAL

Miss Claire Eades
Clinical Academic Fellow
School of Nursing, Midwifery and Health
RG Bomont Building
University of Stirling
FK9 4LA

Dear Miss Eades

Letter of Access: Exploring Postnatal experiences, knowledge and perceptions of women with gestational diabetes 14/ES/0003Research study title

On behalf of NHS Forth Valley Board I am writing to confirm that your Letter of Access for this study has been extended to 01 June 2017, as per the details of the amendment acknowlegement letter issued by the East of Scotland Research Ethics Service on 27 May 2016. All other terms and conditions of the original Letter of Access remain in place.

Please notify **your academic supervisor** of the extension to your Letter of Access.

Yours sincerely

Dr. Rosemary Wilson
Research and Development Officer

INVESTORS IN PEOPLE | Silver

Chairman: Alex Linkston CBE
Chief Executive: Jane Grant

Forth Valley NHS Board is the common name for Forth Valley Health Board
Registered Office: Carseview House, Castle Business Park, Stirling, FK9 4SW

www.nhsforthvalley.com Facebook.com/nhsforthvalley @nhsforthvalley

Appendix 14

Participant consent form for publication 5.

UNIVERSITY OF STIRLING

CONSENT FORM

Title of Project: Exploring postnatal experiences, knowledge and perceptions of women with gestational diabetes

Name of Researcher: Claire Eades

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated 04.02.14 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that it is my choice whether to take part and that I can withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree to my interview being digitally recorded. ☐

4. I understand that anonymised, word for word quotations of what I say may be used in reports of the study ☐

5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from NHS Forth Valley, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent.	Date	Signature

Consent form date of issue: 04.02.14
Consent form version number: 2

Appendix 15

Participant information sheet for publication 5.

UNIVERSITY OF STIRLING

Contact: Claire Eades, c.e.eades@stir.ac.uk, 01786466282

Exploring postnatal experiences, knowledge and perceptions of women with gestational diabetes

My name is Claire Eades and I am required to undertake a project as part of my course and invite you to take part in the following study. However, before you decide to do so, I need to be sure that you understand firstly why I am doing it, and secondly what it would involve if you agreed. I am therefore providing you with the following information. Please read it carefully and be sure to ask any questions you might have and, if you want, discuss it with others including your friends and family. I will do my best to explain the project to you and provide you with any further information you may ask for now or later.

What is the purpose of the study?

We would like to explore what women with gestational diabetes know and believe about this condition after they give birth. It is hoped this will give us a better understanding of any information or support that women with gestational diabetes may need after pregnancy.

Why have I been invited to take part?

You have been invited to take part because you have been identified as someone who has gestational diabetes.

Do I have to take part?

You are under no obligation to take part in the study. If you do not wish to participate your care will not be affected in any way.

What if I change my mind about taking part?

You are free to withdraw from the study at any point without having to offer any explanation. Withdrawal from the study will have no consequences for you or on the care that you receive.

What will taking part in this study involve?

If you agree to take part in the study you will be contacted by telephone around 8 weeks after your due date to arrange a suitable time to take part in an interview with the researcher. We can arrange the interview to take place either at your home or the University of Stirling. Before starting the interview you will be asked again if you agree to take part in the study. The interview will last around an hour and you will be asked to give your views on gestational diabetes. The interview will be recorded with your permission. As soon as the recordings have been written up word for word the recording will be destroyed. Your involvement in the study will end after you complete the interview. If we get too many volunteers for the study we might not need you to take part but we will let you know if this is the case.

Will I benefit from taking part?

The research may be of no benefit to you personally. However, it is hoped that your contribution will help us to improve the information and support given to women who have had gestational diabetes. You will be given a £20 Mothercare voucher as a thank you for your time.

Are there any risks involved in taking part?

Information sheet date of issue: 04.02.14
Information sheet version number: 2

While we think that it is unlikely that you will face any risks from participating in the study it is possible that you may experience some discomfort in discussing your health with someone you do not know. However, you do not have to answer any questions that you do not want to and are free to withdraw from the study at any point without giving a reason.

Will I be able to be identified from the results?

All information you give during the interview will be completely anonymous and you will only be referred to by a number e.g. participant 3. Anything you say that might make it possible to identify you will be altered or removed. Any information that could identify you will be confidential and stored securely and separately from the information you give in the interview. All interview recordings will be destroyed at the end of the study.

What will happen to the results of the research study?

The results of the study will be summarized in verbal and written reports for the health service. The findings may also be presented at conference and may be written up for publication in academic journals. Anonymous quotations of your interview may be used. Anonymity and confidentiality will be maintained in all cases.

Who is organising and funding the research? Who has approved the research?

The research has been organised jointly by staff at NHS Forth Valley and the University of Stirling and is being funded by both organisations. The study has received ethical approval from the School of Nursing, Midwifery and Health. The East of Scotland Research Ethics Service REC 1, which has responsibility for scrutinising all proposals for medical research on humans in Tayside, has examined the proposal and has raised no objections from the point of view of medical ethics. It is a requirement that your records in this research, together with any relevant medical records, be made available to monitors from NHS Forth Valley, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

If you would like any more information on the study please contact the researcher:

Claire Eades, School of Nursing Midwifery and Health, University of Stirling, Tel: 01786 466282, Email: c.e.eades@stir.ac.uk

If you would like to speak to someone who knows about this study who is an independent advisor, please contact:

Dr Ashley Shepherd, School of Nursing, Midwifery and Health, University of Stirling, FK9 4LA. Tel: 01786 466345, Fax: 01786 466333, Email: ashley.shepherd@stir.ac.uk

What happens if I have a complaint about the study?

If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek any resulting compensation through the University of Stirling who are acting as the research sponsor. Details about this are available from the research team. Also, as a patient of the NHS, you have the right to pursue a complaint through the usual NHS process. To do so, you can submit a written complaint to the Patient Liaison Manager, NHS Forth Valley Patient Relations and Complaints Service, Forth Valley Royal Hospital, Stirling Road, Larbert, FK5 4WR (Phone: 01324 566 660). Note that the NHS has no legal liability for non-negligent harm. However, if

Contact: Claire Eades, c.e.eades@stir.ac.uk,
01786466282

you are harmed and this is due to someone's negligence, you may have grounds for a legal action against NHS Forth Valley but you may have to pay your legal costs.

Thank you for taking the time to read this information sheet and considering taking part in this study.

Information sheet date of issue: 04.02.14
Information sheet version number: 2

Appendix 16

Illustrative excerpt from an analytical framework matrix for gestational diabetes mellitus topic theme.

2. GDM	2.1 Identity	2.2 Timeline	2.3 Cause	2.4 Emotional Representations	2.5 Consequences	2.6 Control	2.7 Illness Coherence	2.8 GDM Education	Theme Summary
P1 Age: late 30s Baby age: 3 months Parity: +2 Dep: Middle (3)	Felt very tired but questioned whether the high BG readings were down to eating a lot. *"maybe I didnae have it all, and it was just…well obviously I did "*	Viewed as temporary. "*I don't need to remember that now because I've had her…and she tested fine"*	Caused by diet. *" I'd already set myself down the road to the gestation diabetes…because I was stuffing Mars Bars in my mouth like you wouldnae believe [laugh] for to try and get a bit of energy about me"*	Saw diagnosis as a wake up call but not overly concerned. Mostly concerned about baby rather than herself. *" it doesn't really matter about me."*	Talked about the consequences for her baby and for delivery. *"you see these babies that just look so puffy and…not ill, because they don't look ill, but just sort of…oh my god, what a shame, and I've done that to you, kind of thing. And then step two pops in and you think, how am I gonna to get that out? [Both laugh]. If it's like a twelve pound baby because it's all swollen or"*	Felt it was easy to control with diet. *"they gave me the wee kit for to like, for to test the blood and things. And because you could see it was working, what you were doing"*	No data	Didn't remember much but felt she it was fine at the time. *"It was fine. It wasnae like it was information overload or too technical or anything like that. It was alright, it was alright."*	**Questioned diagnosis and thought it was caused by her diet. Concerned for baby rather than herself. Doesn't seem to have had big impact on her life and found it easy to control. Viewed as temporary.**

P2 Age: early 40s Baby age: 3 months Parity: +1 Dep: Low (4)	Had read about it books about pregnancy. Felt tired. *"I felt that at night time I was getting really tired…and I knew that if I fell asleep early I wouldn't sleep at night"*	N/D	Caused by diet, particularly chocolate eaten to give her energy when she was tired. *" I don't normally eat chocolate and I think that might have triggered…the diabetes"* Besides eating chocolate she felt she was very healthy and so was confused about why she got it and suggests it's just *"one of those things".*	Not scared as saw it as something quite common. *"it was quite common, so…that sort of puts your mind at ease, it didn't scare me or anything. So, it was okay. Knowing that lots of people get it and it was quite normal, and the people at the hospital were really nice…and they spoke you through everything that happens…and it was fine."*	Mentioned the risk of getting GDM again in future.	Found it easy to get under control through diet, particularly cutting out chocolate. *" it was quite easy to get under control…it really was, just, as I said, cutting out the chocolate at night"*	No data	Staff at hospital were nice and didn't make too big a thing about it. Felt she already knew a lot of what they were telling her about diet. *"and then at the hospital they were really, really nice…and they didn't make it a big thing…which you don't need when you're pregnant."*	**Thought it was caused by diet. Found it easy to control and saw it as something quite common so wasn't concerned.**
P4 Age: early 20s Baby age: 6 months Parity: +1 Dep: High (1)	Was thirsty and going to the toilet more. *"Erm, I didn't actually know that you could get diabetes when you were pregnant."*	Viewed as temporary. *"So, it was only for so long and then they're here."*	Caused by diet. *"I had been really quite bad with my food to the extent it led me to get, eh, the gestational diabetes "*	Wasn't too bothered but partner was worried and upset. *"Erm, and...but it didn't really bother me because my wee sister's got diabetes and so has my partner."* *"My partner was quite, erm...he was quite upset"*	Didn't discuss apart from saying partner worried about the chance of the baby having diabetes. "he was saying he didn't want him to have diabetes when he was born and things like that"	Bloods were pretty normal through watching her diet. *"I think, that was probably why my blood was always a lot better. Eh, and why it was never over just because I had changed from just eating sweeties and crisps and basically whatever I wanted to being a bit healthier in my diet again "*	Wasn't something she knew about before pregnancy. *"Erm, I didn't actually know that you could get diabetes when you were pregnant. Eh, I didn't know that was a thing, erm, but it was fine"*	Felt it was explained well and wasn't too complicated.	**Thought it was caused by her diet. Not worried and managed to control through diet. Viewed as temporary.**

Appendix 17

Consolidated COREQ checklist completed for publication 5.

Developed from:

Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

The section numbers refer to the section of the thesis that the information is reported in.

No. Item	**Guide questions/description**	**Reported in Section No.**
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the interview or focus group?	8.4
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	8.4
3. Occupation	What was their occupation at the time of the study?	8.4
4. Gender	Was the researcher male or female?	8.3
5. Experience and training	What experience or training did the researcher have?	8.4
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	8.3
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	8.4
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g.	8.4

No. Item	Guide questions/description	Reported in Section No.
	Bias, assumptions, reasons and interests in the research topic	
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	8.5
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	8.3
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	8.3
12. Sample size	How many participants were in the study?	8.4
13. Non-participation	How many people refused to participate or dropped out? Reasons?	8.4
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	8.4
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	8.4
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Table 14
Data collection		

No. Item	Guide questions/description	Reported in Section No.
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	8.4
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	N/A
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	8.4
20. Field notes	Were field notes made during and/or after the interview or focus group?	8.4
21. Duration	What was the duration of the inter views or focus group?	8.4
22. Data saturation	Was data saturation discussed?	8.3
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	N/A
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	8.5
25. Description of the coding tree	Did authors provide a description of the coding tree?	Table 15
26. Derivation of themes	Were themes identified in advance or derived from the data?	8.5
27. Software	What software, if applicable, was used to manage the data?	8.5
28. Participant checking	Did participants provide feedback on the findings?	N/A
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was	Yes – quotations from different

No. Item	Guide questions/description	Reported in Section No.
	each quotation identified? e.g. participant number	participants presented throughout results section with participant numbers.
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Attempted to make it clear throughout section 8.6 how data links with the findings.
31. Clarity of major themes	Were major themes clearly presented in the findings?	Start of section 8.6 and Figure 5.
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes – throughout results section