NCCHTA

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Technology assessment report commissioned by the NHS R&D Programme on behalf of the HTA Programme.

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1. Title: Non-pharmacological interventions for adults with impaired glucose tolerance.

2. TAR team

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Sue Jick from Boston will assist with the survey of current practice using GPRD data.

3. Plain English summary

Diabetes is characterised by elevated blood glucose levels, and there is international agreement on how high the level has to be before diabetes is diagnosed – a good bit above normal. So some people have blood glucose levels that are not normal, but not diabetic. Some of these people have high glucose levels only after meals, or after glucose tolerance tests (when the body's reaction to a glucose drink is tested). They are said to have impaired glucose tolerance or IGT. Others have high levels while fasting (but their glucose level after a meal may be normal. They are said to have impaired fasting glucose, IFG.
IGT and IFG are important for three reasons. Firstly, they may both progress to diabetes. Secondly, both, though more so IGT, are associated with an increased risk of heart disease. Thirdly, if we were to screen for type 2 diabetes, we would find more people with IGT and IFG, depending on which screening test was used, than with diabetes. Having found them, we need to be able to advise on management.
This review will examine non-pharmacological ways of reducing the risk of IGT and IFG progressing to diabetes, and will also consider ways of reducing the risk of heart disease in people diagnosed with the conditions.
Many will be diagnosed not by screening, but by their own doctors, for example if they are being checked for heart disease risk, or because of a family history of diabetes.

4. Background

The prevalence of diabetes is increasing. In type 1 diabetes, we do not know the cause or causes and therefore it cannot be prevented. However in type 2 diabetes, which makes up about 80% of all diabetes, we know that being overweight or obese greatly increases the risk,

and so much T2DM is theoretically preventable. Exercise may also play a role independently of weight, as well as associated with it.
The prevalence of obesity is also rising. It is likely that if we could prevent some obesity, we would prevent or at least delay, a corresponding amount of T2DM.

Two conditions (which may co-exist) appear to precede T2DM. The first is impaired glucose tolerance, in which fasting glucose is normal but there is post-prandial hyperglycaemia. The definition comes from the oral glucose tolerance test (OGTT). The second is impaired fasting glucose, when the fasting level is raised but the post-prandial level does not reach IGT levels.

Table – plasma glucose levels (mmol/l) and diagnostic categories

	fasting	2-hour OGTT
normal	6.0 or under	<7.8
IFG	6.1 to 6.9	<7.8
IGT	<7.0	7.8 to 11.0
diabetes	7.0 or over	11.1 or over

IFG and IGT have been called “pre-diabetes” but the term is unsatisfactory because not all people with the two conditions go on to develop diabetes. However, about half (REFs) do. So they represent a group in whom intervention may be able to prevent or delay the onset of diabetes.
There are currently discussions in the National Screening Committee and Department of Health about screening for type 2 diabetes. In its early stages, T2DM can cause no symptoms, but can be causing damage to small and large blood vessels.
If there is screening for diabetes, we would expect, depending on method used, to detect as many people with IGT and/or IFG, as with diabetes. Hence before any screening programme starts, we need to decide what to do with those with IGT and IFG.
Possible interventions include drugs such as metformin, but the main focus of this review will be on non-pharmacological interventions. Metformin has been used as an arm in trials of prevention and therefore will be a comparator for some purposes.

5. Decision problem

Key question: are there clinically and cost-effective interventions which will reduce the development of diabetes in those with IGT and IFG?

Interventions to be examined.

5.1 Weight loss in those who are overweight (BMI 26-29) or obese (BMI 30 and over), by calorie restriction, alone or combined with exercise.

5.2 Exercise therapies. Does exercise alone, without weight loss, lead to reduction in risk?

5.3 Qualitative changes in diet – i.e. without calorie restriction and weight loss.

5.4 All of the above depend on compliance, so we will also look for evidence on ways in which adherence to diet and exercise can be improved.

5.5 Ethnic differences. The risk of diabetes is higher in people of South Asian ancestry, and there is some evidence that their exercise habits may differ from indigenous Britons. We will therefore look specifically for trials in this population.

Comparators.

The comparator will be standard care. In primary care, this is changing because of the new contract, but in brief it will be taken as no organised screening; the usual lifestyle advice given opportunistically; and care of diabetes when it becomes symptomatic. However we will carry out a survey of primary care using the GPRD database, to see if there are data on recent practice.

Population and subgroups.

The risk of IGT and diabetes increases steeply with age, and it could be argued that only, say, the over 45s should be included. However it is likely that in addition to diabetes increasing in prevalence, there is also a reduction in age at onset. True T2DM is being seen in children. A counter-argument might be that intervention should therefore be much earlier, in the hope of establishing healthier habits at a younger age that would then persist.
Subgroups of interest will be influenced by the debate on screening, but will include;

- the South Asian population
- those who are overweight as children and young adults
- older age groups, because of the rising prevalence with age.
- possibly, those with other features of the metabolic syndrome such as hypertension, central obesity and high lipids

The remit for the review starts with the fact of IGT and IFG, and is concerned with reduction of progression to diabetes. However inevitably, the costs and benefits of treating IGT and IFG will affect the wider economics of screening, and this is considered in the economics section

We will note and briefly report on any evidence for prevention of IGT and IFG. Strictly speaking that is outwith the remit, but measures to prevent IGT and IFG are probably similar to those for treating them. Similarly if we retrieve trials dealing with people with metabolic syndrome (however defined) but who do not have IGT or IFG, we will note them in passing, since potentially the interventions could reduce later IGT.

6. Methods – clinical effectiveness

The patient group is defined by the remit – those diagnosed with IGT and IFG.

Search strategy.
Some of the topics that need to be considered have been covered by other reviews. Our first step will be to search for reviews, and to identify good quality ones. Their findings will then be summarised.
They will include;

- recent Cochrane reviews, including that by Norris and colleagues on "Long-term non-pharmacological with loss interventions for adults with pre-diabetes"
- The Australian Evidence-based guideline for the primary prevention of type 2 diabetes
- The guide to community preventive services: diabetes and physical activity: Task Force on Community Preventative Services 2002 (USA)
- The New Zealand Health Technology Assessment Centre report on dose, intensity and type of physical activity required to affect risk factors for cardiovascular disease.
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We will then search for primary evidence from more recent studies, not included in previous reviews.
Several key-note studies will have been covered in other reviews, but will be summarised in this review for convenience, and their applicability to the UK considered.
We will search MEDLINE, EMBASE, and all sections of the Cochrane Library. The last two years of the Science Citation Index – for meeting abstracts only – will also be searched.

Our general approach to literature searching will be as follows, looking in sequence at;

1. The epidemiology and natural history of IGT and IFG, to give baseline data against which to judge the interventions. Population-based epidemiological studies will be sought.

2. Effectiveness and cost-effectiveness of lifestyle interventions for "pre-diabetes", IGT and IFG, and "metabolic syndrome" (however defined). We will look for trials of interventions such as physical activity and weight loss, back to 1990. Preliminary investigation indicates that these can be successful in trials. The outcomes here will be progression to diabetes, side-effects, quality of life, cost-efectiveness.

3. Adherence to lifestyle interventions for the above conditions, plus diabetes. Success in routine care may be less than in trials, and so we will look also for reviews and RCTs, back to 1990, which provide evidence on ways of increasing motivation to participate in and persist with such lifestyle changes. Given the problem of volunteer bias, only RCTs will be used for conclusions on effectiveness, but other studies may be included if they help to explain adherence or non-adherence. The outcomes here will be adherence or its converse, drop-out rate.

4. Type 2 diabetes and physical activity. Some evidence from people who already have diabetes may be useful. We will include only reviews from 2000 onwards in this section.

The search strategy below will be run in MEDLINE for studies on the epidemiology and natural history of IGT and IFG
1. incidence/ or prevalence/
2. Epidemiology/
3. Glucose Intolerance/ep [Epidemiology]
4. Prediabetic State/ep [Epidemiology]
5. (impaired glucose intolerance or impaired fasting glucose or prediabet$ or pre-diabet$).tw.
6. (1 or 2) and 5
7. 3 or 4 or 6

The search strategy below will initially be run in MEDLINE (back to 1966) for reviews, RCTs and economic evaluations:

1. exp Prediabetic State/
2. exp Glucose Intolerance/
3. exp Diabetes Mellitus, Type 2/pc [Prevention & Control]
4. Metabolic Syndrome X/
5. (pre-diabet$ or prediabet$ or fasting glucose or impaired glucose tolerance or (elevated adj3 glucose) or glucose intolerance or hyperglycemia or hyperglycaemia or metabolic syndrome or insulin resistance or (risk$ adj2 diabet$)).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp Diet Therapy/
8. Exercise/
9. exp Life Style/
10. ((prevent$ adj3 diabet$) or non-pharmacological or non-drug or (diet$ adj3 weight loss) or exercise or life-style or life style or physical activity).tw.
11. 7 or 8 or 9 or 10
12. randomized controlled trial.pt.
13. random$.tw.
14. meta-analysis.pt.
15. (systematic review or systematic overview).tw.
16. 12 or 13 or 14 or 15

17. 6 and 11 and 16
18. limit 17 to english language

This strategy will then be combined with appropriate search filters for systematic reviews, RCTs, and economic evaluations. The search strategy will then be adapted as appropriate and run in the other databases mentioned above.

The search will be limited to English language only.

If further relevant search terms or interventions become apparent during the course of review then the above strategy may be modified.

In addition, the National Research Register will be checked for ongoing studies and contact may be made with key authors for unpublished data.

Inclusions and exclusions

The focus will be on lifestyle interventions such as diet and physical activity. Gastric surgery for morbid obesity will not be included (but we will summarise and refer to previous reviews such as the HTA monograph).
Because the interventions relevant to this review are lifestyle ones, only RCTs will be included because of the risk of bias in non-randomised studies, such as volunteer bias (people willing to take part, and to persist with, trials of weight loss or exercise, may have been going to do better without the intervention, so randomisation to intervention or control groups is essential).
Trials of less than 2 years duration will be excluded. Ideally, we would like follow-up of 10 years or more.
We will prefer UK-based studies for prevalence and natural history but will use with caution studies from countries with a similar ethnic and socio-economic mix (Australia, New Zealand).
Studies in the general population may not be applicable to people diagnosed with IGT, partly because of the effect of the diagnosis, partly because of associated factors such as overweight.

Study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, involving a third reviewer if necessary.

Outcomes of interest

Primary outcomes

- prevention of diabetes in those with IGT and IFG
- regression from IGT and IFG to normal blood glucose levels
- cardiovascular mortality and morbidity

Secondary outcomes (mainly affecting cardiovascular risk);

- weight loss of 5kg or more if sustained for more than 2 years.
- significant reduction in plasma cholesterol (% with TC under 5.2 mmol/l, or with drops of 1 mmol/l or more)
- reduction in blood pressure
- costs of health care

Compliance with interventions will not of itself be used as an outcome.

Data extraction strategy

Data will be extracted independently by two reviewers using pre-defined data extraction forms. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

Quality assessment of reviews and trials.

The quality of each study will be assessed by one reviewer. Uncertainties will be discussed with a second reviewer. Criteria used will be those from CRD report number 4, amended if necessary.

Analysis and reporting

The results of good quality reviews will be reported in a narrative form. If there are differing conclusions amongst these reviews, the reasons will be explored.
The results of trials will be reported, summarised in table form, and may be presented in a meta-analysis if appropriate.
Information on prevalence and natural history will be reported in narrative form.

7. Cost-effectiveness

Existing economic studies will be reviewed. Evidence on the increased lifetime costs of diabetes, compared to being non-diabetic and pre-diabetic , will be sought from published literature and models.

Assuming that there is evidence of clinical effectiveness – that intervention can prevent or delay progression to diabetes – the interventions will be costed from the perspective of the NHS. Intervention could be double, in the sense of there being a compliance intervention to improve adherence to a lifestyle one.

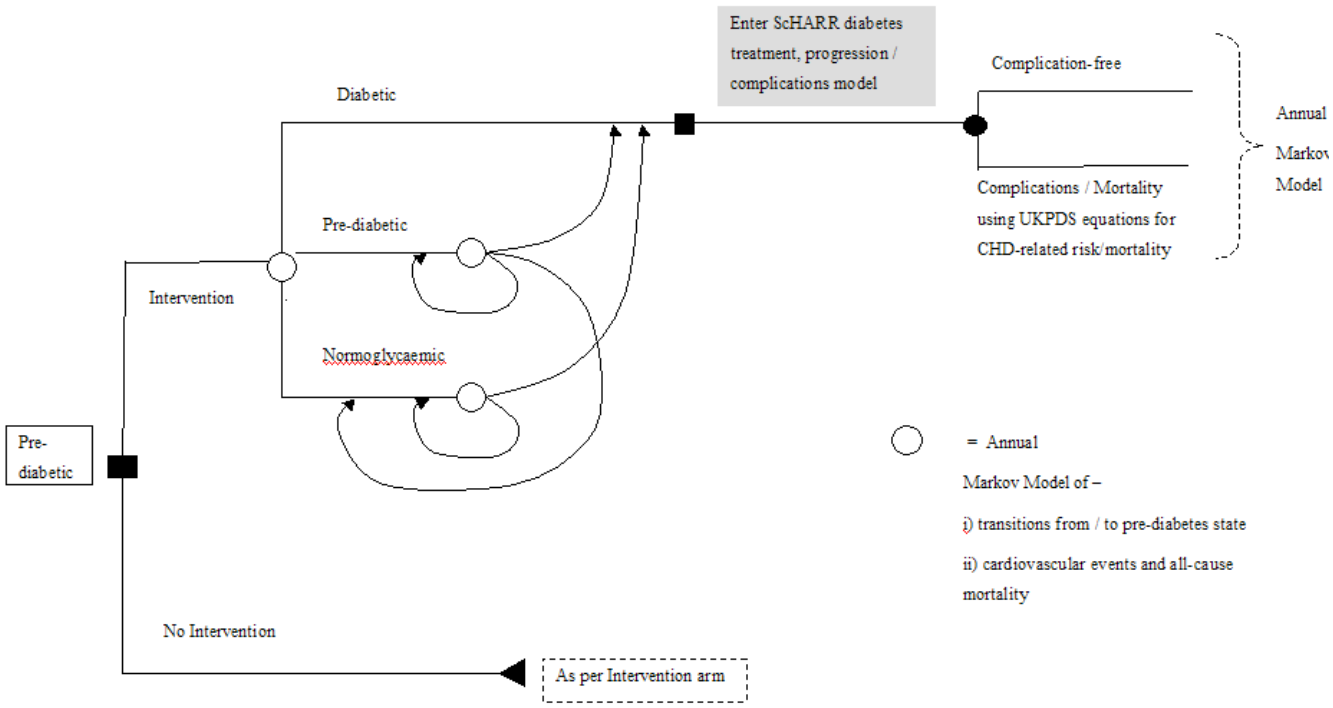
As a first step, the cost per case of diabetes prevented, or of at least two-year delay in onset, will be calculated. The two year period is really too short but we are pessimistic about finding evidence from long-term (e.g. 10 or more years).
Secondly, the monetary savings over a life-time from prevention or delay will be estimated.
Thirdly, the disutility from being diabetic will be derived from published literature and the impact on quality of life estimated; the benefits of prevention can then be expressed in QALY gains.
Fourthly, cost per QALY will be estimated. Costs and QALYs will be discounted by 3.5%
We will consider patient costs such s time, and any costs of diet or exercise. We will also consider, if data appear, any benefits to other family members.
We will not develop a long-term diabetes economic model. Diabetes models are complex, and several tried and tested ones already exist. We will renew a previous collaboration with ScHARR, who have a well-developed model of type 2 diabetes

An outline of the draft model structure is shown below. The three main components are –

i) an annual markov model representing transitions from normoglycaemic and pre-diabetic states to one of these or to diabetes
ii) a diabetes progression model that predicts risk such cardiovascular events and mortality and other-cause mortality
iii) a risk model for cardiovascular events in normoglycaemic and pre-diabetic states

Possible progression pathways include :

IGT > diabetes and later > cardiovascular disease
IGT > cardiovascular disease but without diabetes
IGT > both diabetes and CVD.



Intervention to reduce the risk of progression to diabetes, would probably increase the rate of regression from IGT to normality. That would not affect diabetic outcomes, but would affect cardiovascular ones. The Sheffield model will be expanded to add an IGT locus but also a normality one. We will need to do some literature reviewing specifically to populate the economic model.

Cardiovascular risk in the normoglycaemic and pre-diabetic states will need to incorporate traditional risk factors such as blood pressure and cholesterol, and in particular, a relationship between glucose (and possibly weight ??) and CHD risk. This is important as pre-diabetic patients have a significantly elevated CHD risk compared to the general population. The best mechanism for this needs further consideration but might involve using data from the DECODE study to modify risks obtained from Framingham or the UKPDS risk equations.

Sensitivity analyses will undertaken to identify which variables contribute most to uncertainty in the results, and a restricted probabilistic sensitivity analysis (PSA) will be undertaken (unless cost effectiveness is demonstrated across all sensitivity assumptions). Colleagues at Sheffield have developed methods for substantially reducing the computational burden of using PSA in models.

8. Survey of current practice.

A survey of current recorded prevalence, regression, persistence and progression, of IGT and IFG, and of treatments given, will be undertaken using the UK General Practice Research Database (GPRD). The GPRD is one of the largest longitudinal primary care records database, anonymised and used for research. Since 1988, over 4 million residents of the United Kingdom have registered with more than 300 GP practices that provide data for the GPRD. Details of patient characteristics, treatments prescribed and clinical diagnoses are available. GPRD has been used extensively for research in drug therapy and outcomes in people with diabetes mellitus. It has not, to the best of our knowledge, been used to identify people with pre-diabetic states.

The aims of this survey will include:
Establishing if people with IGT and IFG are identified by their GPs and that information is recorded in the GP records. The fitness of GPRD data for this purpose is not known at present. This survey will provide useful insight into how well this condition is currently recognised and recorded by GPs; providing relevant information to inform policy regarding approaches to the management of potentially pre-diabetic states.
Estimate the prevalence of IGT and IFG recorded in UK general practice and trends in recording over time
Describe the characteristics of people reported to have the conditions including evidence of other components of a metabolic syndrome, clinical management, and disease progression (or regression).

We would focus on GPRD data from 2000 to 2005 in order to be able to describe current clinical practice but will also look at historical data to describe trends and if possible follow people with IGT and IFG diagnoses to describe disease progression.

The coding system available to GPs using the GPRD does include a code for impaired glucose tolerance, and also for "pre-diabetes" (which we have tended to avoid because not all people with IGT or IFG progress to diabetes). We propose to use this code, as well as looking for combinations of codes such as abnormal glucose in the absence of a prior diagnosis of diabetes mellitus (Table 2). Once potential cases have been identified using this screening approach, we will review patients' computer records to classify people as:

Probable IGT or IFG
Possible IGT or IFG

- *IGT or IFG excluded*

For each "probable" or "possible" case, details of follow up, treatment, and outcomes would be recorded. Other metabolic syndrome risk factors will be noted.

Total GPRD population counts will also be obtained in order to allow us to estimate age specific rates of IGT and IFG.
Table 2 Examples of READ codes that could be used in combination with the absence of a prior code for diabetes mellitus to "screen" the GPRD for potential cases

Code	**Terms**
1408.00	at risk of DM
212 6300	DM resolved
R102.11	Pre-diabetes
R102.00	GTT abnormal

R102.12	Impaired GTT
44U5.00	Blood glucose 7-9.9
44U6.00	Blood glucose 10-13.9
44UZ.00	Blood glucose 14+
44U9.00	Blood glucose abnormal
44Uz.00	Blood glucose raised
44Uz.11	hyperglycaemia
44V2.00	GTT impaired
44V3.00	GTT abnormal
R105700	Blood glucose abnormal

The cost of this will be £10,000. We will use existing links with one of the groups with most experience with GPRD, in Boston, Professor Herschel Jick and colleagues. Corri Black, who will lead this part of the work, spent a year in Boston earlier in her career. We have written to Professor Kent Woods outlining this potential collaboration and explaining that although we would like to use GPRD for appropriate TAR work, our expected use would be too occasional to justify a separate licence, and that our preferred provider is the Boston group. Professor Jick met Professor Woods at MHRA recently, to discuss future use of GPRD. Professor Woods is happy that the Boston group can do the work required under the terms of their existing licence.

9. Collaborations and costs

9.1 A group in the Aberdeen Medical School has secured a contract for a review of interventions in obesity. Following discussion, the timescale for that review will be compatible with our one. This should reduce the work involved.

9.2 The Scottish Evidence-based Child Health Unit has carried out a review of prevention of obesity in childhood. IGT and IFG are probably rare in children, but obesity is becoming more common, so this assumption may not be justified. Data on prevalence will be sought. Key points from the SEBCHU review will be summarised in our review, either in the main text or as an appendix, depending on perception of relevance.

9.3 The recent review of screening for type 2 diabetes covered some issues that relate to this review, and this will also offset the time costs.

9.4 Several other reviews are likely to be useful, and as already mentioned, will be summarised. This “review of reviews” may reduce the number of primary studies requiring to be data-extracted, hence offset the cost of this TAR, and enable us to transfer some funds to the GPRD survey.

9.5 As regards the modelling, colleagues in ScHARR will extend their model, run it to provide data, and we will write it up in collaboration.

Timesheets and contract bills would be kept and the final cost calculated, in terms of TAR units. We would endeavour to keep within a 1.0 TAR unit budget but would welcome some flexibility if necessary. The request in the commissioning brief for a survey is outwith the usual scope of a TAR.

10. Timelines

Final protocol sent to NCCHTA on 28th August.
Literature searches by 3rd August

Clinical effectiveness review August to October.
Survey of current practice using GPRD, by mid-October.
Cost-effectiveness review and modelling September to October
Draft sent out for peer review by end of November
Comments back by late December
Final draft to NCCHTA by end of January.