

# National Evidence Based Guidelines for the Management of Type 2 Diabetes Mellitus

## Part 3

### Case Detection and Diagnosis of Type 2 Diabetes

Prepared by  
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for the Diabetes Australia Guideline Development Consortium

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**Australian Government**

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**National Health and Medical Research Council**

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## PART 3

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# 1.0 Case Detection and Diagnosis Expert Working Group

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## 2.0 Guideline for Case Detection and Diagnosis

### 2.1 Introduction

#### **Aim of the Guideline**

This Guideline addresses the topic of case detection and diagnosis of undiagnosed Type 2 diabetes in asymptomatic non-pregnant adults. It targets all categories of clinicians but will have particular relevance to GPs.

In addition, specific aspects of the Guideline target different audiences. For example, the diagnostic criteria will be applicable to pathology services, and the risk factor information can be used by Aboriginal Health Workers, community health nurses, a wide range of health promotion initiatives, and by targeting people with Type 2 diabetes to ensure that their relatives are aware of who should be tested.

#### **Methods**

In addition to the methods used to identify and critically appraise the evidence to formulate the guideline recommendations described in detail in *Part 1* of the document:

- the Project Management Team reviewed and checked each step of the methods process
- a selection of the searches were repeated
- double culling of the yield was carried out for a selection of the database searches
- one of the Co-Chairs of the Case Detection and Diagnosis EWG (SC) double reviewed all the articles used as evidence references
- the Project Management Team checked all recommendations, evidence statements, evidence tables
- the Project Management Team documented and checked all the information supplied in the search strategy and yield tables

#### **Guideline Format**

Issues identified by the EWG and from the literature as critical to case detection and diagnosis of Type 2 diabetes are shown in point 2.2 ( next page).

*Each of these issues* is addressed in a separate Section in a format presenting:

- ***Recommendation(s)***
- ***Evidence Statements*** - supporting the recommendation(s)
- ***Background*** - to the issue under consideration
- ***Evidence*** - detailing and interpreting the key findings
- ***Summary*** - of major evidence found
- ***Evidence tables*** - summarising the evidence ratings for the articles reviewed

*For all issues combined*, supporting material appears at the end of the guideline topic and includes:

- ***Evidence references***
- ***General references***
- ***References identified***

## 2.2 Issues for Case Detection and Diagnosis

- Is case detection and diagnosis of Type 2 diabetes worthwhile?
  
- Who should be tested for undiagnosed Type 2 diabetes?
  
- How should case detection and diagnostic testing for Type 2 diabetes be performed?
  
- How often should testing be performed?

## 2.3 Summary of Recommendations

### Recommendation

Active case detection and diagnosis of Type 2 diabetes should be considered for the following reasons:

- Type 2 diabetes is a serious and costly health problem
- The natural history of Type 2 diabetes includes an asymptomatic phase which is not benign and during which it can be diagnosed
- Early treatment of Type 2 diabetes reduces morbidity from long term complications
- Case detection and diagnosis of Type 2 diabetes has a favourable risk:benefit ratio

Although the health impact of Type 2 diabetes is significant, its overall prevalence does not justify universal testing of the entire Australian adult population. Rather, opportunistic case detection is recommended using the following procedures:

Testing for undiagnosed Type 2 diabetes is recommended for the following high risk individuals:

- People with impaired glucose tolerance or impaired fasting glucose;
- Aboriginal and Torres Strait Islanders aged 35 and over;
- Certain high risk non-English speaking background groups aged 35 and over (specifically Pacific Islander people, people from the Indian subcontinent or of Chinese origin);
- People aged 45 and over who have either or both of the following risk factors:
  - obesity (BMI  $\geq$  30 );
  - hypertension;
- All people with clinical cardiovascular disease (myocardial infarction, angina or stroke); and
- Women with polycystic ovary syndrome who are obese.

Individuals presenting the following risk factors are also considered to be at high risk of having undiagnosed Type 2 diabetes but further studies are required in order to evaluate any net clinical or economic benefit of testing these groups:

- Women with previous gestational diabetes;
- People aged 55 and over; and
- People aged 45 and over who have a first degree relative with Type 2 diabetes.

An economic analysis should be undertaken to evaluate the benefits of screening for undiagnosed Type 2 diabetes in women with a previous history of gestational diabetes, people aged 55 and over, and for people aged 45 and over who have a first degree relative with Type 2 diabetes.

Measure plasma glucose as the screening test in people with risk factors. This should be performed by a laboratory (rather than with a blood glucose meter) and should preferably be done on a fasting sample. However a random measurement may be used

The plasma glucose results should be interpreted as follows:

- less than 5.5 mmol/l – diabetes unlikely
- 7.0 mmol/l or more fasting or 11.1 mmol/l or more random – diabetes likely
- between 5.5 and 6.9 mmol/l fasting or between 5.5 and 11.0 mmol/l random, perform an oral glucose tolerance test
- the oral glucose tolerance test should be performed and interpreted according to the 1999 WHO criteria

A confirmatory test must be performed on a separate day to confirm the diagnosis in all asymptomatic individuals whose results are suggestive of a diagnosis of diabetes

Periodic retesting for undiagnosed Type 2 diabetes is recommended by measuring fasting plasma glucose according to the following schedule:

- each year for people with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
- every 3 years for people at high risk\* with a negative screening blood test
- people with an initial plasma glucose consistent with a diagnosis of diabetes or IGT/IFG which is not confirmed on subsequent testing should be retested after 1 year

\* High Risk is defined on p139

All people with identified risk factors for Type 2 diabetes who have a negative screening test are at risk of cardiovascular disease and the future development of Type 2 diabetes, and should be given appropriate advice on risk factor reduction

## 2.4 Recommendations

# Section 1: Case Detection and Diagnosis

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### Issue

**Is case detection and diagnosis for Type 2 diabetes worthwhile?**

### Recommendation

Identify and treat Type 2 diabetes at a stage before clinical presentation in order to reduce morbidity from long term complications.

### Evidence Statements

- Type 2 diabetes is a serious and costly health problem  
*Evidence Level III-2*
- The natural history of Type 2 diabetes includes an asymptomatic preclinical phase which is not benign and during which it can be diagnosed  
*Evidence Level III-2*
- Early treatment of Type 2 diabetes reduces morbidity from long term complications  
*Evidence Level II*
- Case detection and diagnosis of Type 2 diabetes has a favourable risk:benefit ratio  
*Evidence Level III-2*

## Background – Why Detect Type 2 Diabetes

The recently released findings of the Australian national prevalence study, AusDiab (the Australian Diabetes, Obesity and Lifestyle Study), show that Type 2 diabetes affects 7.5% of the Australian population in people aged 25 years or older and confirm that there is one undiagnosed for every diagnosed person with Type 2 diabetes (Zimmet et al, 2000). Diabetes, both diagnosed and undiagnosed, is a major independent risk factor for cardiovascular disease, blindness, renal failure and lower limb amputation. Since many people with Type 2 diabetes have the disease for a number of years before it becomes clinically apparent, active case detection of asymptomatic individuals is the only way of uncovering their disease. Nearly 80% of people with undiagnosed Type 2 diabetes have readily identifiable risk factors (Cowie et al, 1994) and over 90% visit a doctor (predominantly a general practitioner) each year (ABS,1997a). Opportunistic case detection in the primary health care setting therefore provides the opportunity to identify the estimated 300 000 to 500 000 Australians (ABS,1997b; Zimmet et al, 2000) with undiagnosed Type 2 diabetes.

This Section discusses and evaluates the merits of case detection and diagnosis of undiagnosed Type 2 diabetes in non-pregnant adults.

Case detection can be justified if a disease represents an important health problem, is present at a high enough prevalence (within the total or a specific target population), has a relatively long asymptomatic phase, and interventions are available which have a proven beneficial effect on clinically meaningful outcomes. Furthermore, the test for the disease must be safe, acceptable to the target population and have adequate sensitivity and specificity. Ideally any case detection program should be assessed in randomised controlled trials measuring health outcomes and costs in screened and unscreened populations. In the absence of such information, case finding is considered worthwhile if all or most of the above requirements are fulfilled.

Type 2 diabetes is both a disease entity and a risk factor for other disease, predominantly cardiovascular and cerebrovascular disease. Consequently, both aspects should be considered in evaluating recommendations for active case detection of undiagnosed Type 2 diabetes.

Screening for Type 2 diabetes in asymptomatic individuals has been under consideration for many years (Dowse et al, 1997). There is general agreement that universal screening is not justified. The largest study of this kind tested over 600 000 people in Cleveland, USA, and concluded that indiscriminate mass screening programs for diabetes was of questionable value and that such programs should be directed to targeted population testing (Houser et al, 1977; Genuth et al, 1978).

A number of organisations have considered and made recommendations about selective screening for Type 2 diabetes. Some have concluded that selective screening of individuals with risk factors may be reasonable (American College of Physicians, 1991; American Academy of Family Physicians, 1994; Canadian Task Force, 1994). The US Preventive Services Task Force (Carrington-Reid et al, 1996) concluded that there was insufficient evidence to recommend for or against routine testing for diabetes in asymptomatic individuals but that clinicians may decide to screen persons at high risk of diabetes. On the other hand, both the American and Canadian Diabetes Associations recommend testing in high risk individuals (Canadian Diabetes Association, 1998; ADA, 2000).

However the recent release of the results of the landmark United Kingdom Prospective Diabetes Study (UKPDS 33, 1998) have conclusively demonstrated the beneficial effects of

intervention in people with newly diagnosed Type 2 diabetes. Also our understanding of the natural history of Type 2 diabetes has expanded. With this new knowledge, it is both appropriate and timely to revisit the question of case detection and diagnosis of Type 2 diabetes.

## Evidence – Why Detect Type 2 Diabetes

### **Type 2 diabetes is a serious and costly health problem**

Type 2 diabetes is a serious and increasing health problem in Australia (McCarty et al, 1996) which can result in major irreversible long term complications including myocardial infarction, stroke, retinopathy and blindness, renal disease requiring dialysis or transplantation, neuropathy, foot ulcer, amputation, and erectile dysfunction. The 1998 National Association of Diabetes Centres Data Collection (NADC, 1999) found an annual incidence among adults of 4.6% for myocardial infarction, 2.4% for stroke, 1.1% for amputation, 1.2% for dialysis/transplantation and 0.8% for new blindness. Also, people with diabetes have a reduced life expectancy, predominantly related to cardiovascular complications which occur at 2-4 times the rate of people without diabetes (Colagiuri et al, 1998).

In addition to Type 2 diabetes, less severe abnormalities of glucose tolerance are also associated with increased morbidity and mortality. Impaired Glucose Tolerance (IGT) defines a subgroup of the population which has glucose levels intermediate between normal values and those diagnostic of diabetes. People with IGT are at increased risk of the future development of Type 2 diabetes and also at increased risk of cardiovascular disease morbidity and mortality (Alberti, 1996).

IGT is common with prevalence rates in the USA increasing from 13% for people aged 35-45 years, 24% in the 45-55 year old age group and 40% in 65-74 year old people (Harris, 1993). In the 1981 Busselton study 4.3% of men and 3.3% of women had IGT (Glatthaar et al, 1985) and in the Victorian country study rates of 4.0% in men and 7.8% in women were observed with similar rates in Aboriginal people (Guest et al, 1992). However, the preliminary results of AusDiab suggest considerably higher current rates of IGT in Australia (Zimmet et al, 1999a). Approximately one third of people with IGT will develop Type 2 diabetes (WHO, 1994).

The annual total costs of diabetes in Australia have been calculated to be \$1 billion (McCarty et al, 1996). Diagnosed diabetes was the 7<sup>th</sup> leading cause of burden of disease in Australia in 1996, accounting for 5.4% of the total attributable burden of disease (Mathers, 1999) of which 3.1% was due to diabetes and its sequelae and the other 2.3% was attributable to diabetes as a risk factor for coronary heart disease and stroke. These figures almost certainly underestimate the situation because of the high prevalence of undiagnosed Type 2 diabetes and the well documented failure to record diabetes as a contributing factor to cardiovascular mortality and morbidity. A number of international studies have shown remarkably similar results in reporting that the estimated 4% of the population which has diabetes accounts for 12% of the total health care expenditure (Colagiuri et al, 1998).

## **The natural history of Type 2 diabetes includes an asymptomatic preclinical phase which is not benign and during which it can be diagnosed**

### **1. *Natural history of Type 2 diabetes:***

Studies which have examined the relationship of diabetes complications and the diagnosis of diabetes indicate that Type 2 diabetes commonly has a lengthy asymptomatic phase.

Microvascular complications are commonly present at the time of diagnosis of Type 2 diabetes in both symptomatic and asymptomatic individuals. Various studies have reported retinopathy in 9.9-29% of people at the time of diagnosis of Type 2 diabetes (Harris, 1993) including rates of 14.2-18.8% in newly diagnosed subjects detected during screening surveys, while neuropathy is found in 9% (Harris, 1993) and diabetic renal disease in 5-10% (Ballard et al, 1988; Haffner et al, 1989).

Duration of diabetes is an important determinant of the prevalence of diabetic retinopathy (NHMRC, 1997). Since approximately 20% of people with newly diagnosed Type 2 diabetes have retinopathy and the increase in prevalence plotted against duration is linear, extrapolation of the line to zero prevalence of retinopathy indicates that retinopathy is detectable 6.5 years before diagnosis of Type 2 diabetes (Harris et al, 1992). Furthermore, it is estimated that the minimum duration of diabetes necessary for the development of retinopathy is approximately 5 years (Jarrett, 1986). Therefore, combining the time between onset of diabetes and development of retinopathy of approximately 5 years, and the interval between detectable retinopathy and clinical diagnosis of diabetes of 6.5 years, undiagnosed diabetes may exist for as long as 12 years before clinical diagnosis (Harris et al, 1992).

### **2. *A significant proportion of the population has undiagnosed Type 2 diabetes:***

A number of studies have shown that, across different ethnic groups, approximately 50% of people with Type 2 diabetes are undiagnosed (Harris, 1993). In the US NHANES II survey the prevalence of undiagnosed diabetes increased from 1% in people aged 20-44 years to nearly 10% in people aged 65-74 years (Harris et al, 1987).

Recent Australian population studies which have used a standard oral glucose tolerance test (OGTT) to detect undiagnosed Type 2 diabetes confirm this finding. Guest et al (1992) found 53% previously undiagnosed diabetes among non-Aboriginal Australians in country Victoria. The ratio of undiagnosed to diagnosed cases for Aboriginal people was 0.54. The preliminary findings of AusDiab which has completed testing in Victoria, Western Australia, New South Wales and Tasmania of 6 382 people aged 25 or older, confirm that 50% of people with Type 2 diabetes have previously undiagnosed diabetes (Zimmet et al, 2000).

### **3. *Undiagnosed Type 2 diabetes is not a benign condition:***

People with undiagnosed Type 2 diabetes or lesser impairments of glucose tolerance (IGT and IFG) demonstrate increased morbidity and mortality. The increased morbidity associated with microvascular complications (retinopathy, neuropathy, renal disease) has been discussed previously.

Type 2 diabetes detected by a case detection program is associated with increased mortality and macrovascular events, the major cause of premature death and morbidity in diabetes. In the Melton Mowbray study (Croxson et al, 1994) the age and sex adjusted relative risk of death over 4.5 years compared with people with normal glucose tolerance was 5.2 in people with known diabetes, 3.0 in people newly diagnosed through a detection program for Type 2 diabetes and 1.7 in people with IGT. The DECODE study included data on over 25 000 people from a range of European countries (DECODE, 1999a). Over a mean follow up period

of 7.3 years the hazards ratio for death for people with Type 2 diabetes diagnosed through a case detection program was approximately 2 compared to people with normal glucose tolerance. Similar findings were reported in the Cardiovascular Heart Study (Barzilay et al, 1999) which included 4 515 people over age 65 years. During a mean follow up period of 5.9 years, this study demonstrated an excess of myocardial infarction, stroke and cardiovascular death in people found to have Type 2 diabetes by an OGTT screening program. These recent studies confirm the finding of previous studies - NHANES II (Harris, 1993), the Paris Prospective Study (Eschwege et al, 1985) and the Whitehall study (Jarrett & Shipley, 1988).

### **Early treatment of Type 2 diabetes reduces morbidity from long term complications**

Recent studies have demonstrated the beneficial effects on some diabetes complications by improving metabolic control in people with Type 2 diabetes. The largest and most recent study, the UKPDS, studied over 5 000 people with newly diagnosed Type 2 diabetes. Over a median follow up period of 10 years, the intensively treated group showed a 12% lower risk of any diabetes related end point ( $p=0.029$ ), a 25% reduction in microvascular end points ( $p=0.0099$ ) and a 16% reduction in myocardial infarction which just failed to reach significance ( $p=0.052$ ) (UKPDS 33, 1998).

Studies of people with established Type 2 diabetes confirm the findings of the Diabetes Control and Complications Trial in people with Type 1 diabetes (DCCT Research Group, 1993), that better longer term outcomes are achieved with prevention of the development of complications compared with attempting to prevent the progression of early complications (Abaira et al, 1995; Ohkubo et al, 1995).

The UKPDS study included both symptomatic and asymptomatic people with newly diagnosed diabetes. Whether the treatment benefits apply equally to both groups has not yet been assessed. One recent intervention study from Germany suggests better medium term outcomes in people identified by a case detection program compared with controls (Schneider et al, 1996).

Another potential benefit of early diagnosis of Type 2 diabetes and the early institution of measures to improve glycaemic control, is the delay in the progressive deterioration of beta cell function which characterises Type 2 diabetes (UKPDS 16, 1995) and which results in a progressive increase in treatment required to control the diabetes.

### **Detection and management of preclinical disease results in improved outcomes**

The potential benefit of early detection of Type 2 diabetes has not been evaluated by a randomised intervention in a screened and unscreened population. Recently, data from the UKPDS has been used to address this issue (Colagiuri et al, 2000). UKPDS participants with Type 2 diabetes detected as an incidental finding had a median fasting plasma glucose (FPG) of 10.2 mmol/l and were estimated to have had their diabetes diagnosed 2-3 years earlier than people presenting with symptoms or other clinical manifestations of diabetes (median FPG 12.1 mmol/l). However, complications at presentation and outcomes during the course of the 10 year study were not different in the two groups. On the other hand people who presented with an FPG less than 7.8 mmol/l were estimated to have their diabetes diagnosed 5-6 years earlier than those presenting with an FPG of more than 10 mmol/l. The group with the FPG less than 7.8 mmol/l had significantly less complications at diagnosis and during the course of the study, had less diabetes-related complications, diabetes-related deaths, all-cause mortality, myocardial infarction, lower extremity amputation or death from peripheral vascular disease, microvascular complications, progression of retinopathy and development of peripheral neuropathy and microalbuminuria compared with the group with an FPG of more than 10 mmol/l. The intermediate group with an FPG between 7.8 and 10 mmol/l also

demonstrated significantly lower risk for all complications except for myocardial infarction and stroke compared with the highest FPG group. These data support the concept that an earlier diagnosis of Type 2 diabetes is associated with improved outcomes. However, these benefits require relatively early diagnosis of the diabetes with FPG below 10 mmol/l and preferably below 7.8 mmol/l. Since the majority of people in these categories were asymptomatic at presentation, active case detection programs would be required to detect people with undiagnosed Type 2 diabetes at a stage when intervention could improve outcomes by reducing mortality and macrovascular and microvascular complications.

### **Other potential benefits of case detection programs for Type 2 diabetes**

- People with Type 2 commonly have other risk factors for cardiovascular disease eg hypertension. Identifying undiagnosed diabetes places these individuals in a higher risk category for cardiovascular disease which may prompt earlier, more aggressive or more appropriate treatment of these other risk factors (Goyder & Irwig, 1998a).
- Testing for Type 2 diabetes enables the detection of people with IGT and IFG, conditions associated with increased morbidity and mortality, predominantly due to cardiovascular complications (Alberti, 1996; Barzilay et al, 1999; DECODE, 1999a). Identification of people with IGT and IFG provides an opportunity to implement interventions which may improve outcomes. Intervention studies are currently in progress to test this hypothesis.
- People with IGT have an increased risk of progressing to Type 2 diabetes and a number of studies have shown that the rate of progression can be reduced by lifestyle interventions (Alberti, 1996; Pan et al, 1997)

### **The case detection procedure**

Sections 2 and 3 of this guideline propose opportunistic case detection in high risk individuals using measurement of plasma glucose as the initial test.

Plasma glucose measurement is a safe, easy and relatively low cost test, especially when combined with blood collection for other tests. There are well established and accepted diagnostic criteria for making a diagnosis of Type 2 diabetes (ADA, 1997; WHO, 1999). The properties of the screening and diagnostic procedures are also considered in Section 3.

### **Benefits and harms of case detection**

#### ***Potential Benefits:***

The potential benefits of case detection for asymptomatic Type 2 diabetes have been considered in the preceding paragraphs.

#### ***Potential Harms***

- Medical

Case detection may involve additional testing depending on whether or not the test is performed along with other pathology testing. The diagnostic testing of people with a positive screening test also requires additional testing. Other medical consequences of a diagnosis of Type 2 diabetes or IGT include a variety of treatments (dietary, counselling and possibly medication) and follow up visits to health professionals. If medications are used there is the additional potential for side effects.

Case detection may also result in a false negative result and failure to appropriately treat a person who has diabetes but in whom the diagnosis is missed.

- Psycho social

A diagnosis of Type 2 diabetes has potential implications for employment and personal insurance. Treatment with certain medications, especially insulin, preclude certain forms of employment, related predominantly to the risk of hypoglycaemia and the potential for harm to self and others. Insurance premiums for people with diabetes are invariably substantially higher than in people without diabetes. Perhaps the greatest concern is the false positive result and the anxiety which this may cause in the interval between the initial screening test and the diagnostic test. These aspects of screening have been reviewed by Bastian et al (1998), but there were no data specifically examining these issues in diabetes.

### **Cost analysis**

A comprehensive cost-benefit analysis of screening programs for diabetes should consider the impact on the individual being screened, on the health services and on the community (Dowse et al, 1997). Although there is a lack of precise data about many of these issues, data are available on some aspects of costs associated with case detection and diagnosis for Type 2 diabetes.

The Australian Diabetes Screening Study (Welborn et al, 1997) used a case detection and diagnosis strategy based on opportunistic testing of high risk people presenting to general practitioners for routine visits. Testing procedures included a random plasma glucose and a diagnostic oral glucose test for individuals with a random plasma glucose result over 5.5 mmol/L. Using the data from this study, the cost of identifying each new case of Type 2 diabetes or IGT was \$535 (Colagiuri et al, 1998). A recent theoretical cost analysis performed by Easton & Segal (1998) concluded that the cost of opportunistic screening of obese Italian-born people aged 45 years or over was \$183 for each new case of Type 2 diabetes and IGT. Despite these differences, the cost of screening is relatively small compared to the potential savings from minimising the development of diabetes related complications.

No studies have directly compared outcomes in screened and unscreened populations, but two recent studies have addressed this question using computer modeling. In one study (CDC, 1998), the cost per quality-adjusted life-year (QALY) gained by a one time opportunistic population screening of all people over age 25 was calculated. Risks of complications were derived from a variety of epidemiological studies, and the impact of treatment on microvascular complications was calculated from DCCT data. Macrovascular complications were not considered. The cost/QALY (US\$56 649 per QALY gained) was judged to be acceptable (ie comparable to that of screening for other diseases), and lowest in young people and among African Americans. In the other study (Goyder & Irwig, 2000), the health difference (measured in QALY's) between a screened and an unscreened population of people aged 45-60 was calculated, and the negative impact of screening was included. DCCT data were used to calculate the reduction of microvascular complications, while it was assumed that treatment for diabetes would have a similar impact on macrovascular disease as does treatment for hypertension and hyperlipidaemia. Screening led to a net benefit of 10 QALY's for every 10 000 people screened, mainly from fewer cardiovascular events.

Based on data derived from the CDC model (CDC, 1998), Engelgau et al (2000) in a recent review of screening for Type 2 diabetes concluded that compared with screening for other conditions, diabetes screening is less favorable than some and more favorable than others. Screening and treating persons with no cardiac history with statins ranges from US\$54,000 per QALY to US\$1,400,000 per QALY while screening for breast cancer costs US\$150,000 per QALY, colon cancer US\$16,000 per QALY in persons 50-75 years of age, and cervical cancer US\$16,000 per QALY by pap smear every 4 years for women 20-75 years of age (for every year the figure is >US\$1,600,000/QALY). Consensus indicates that interventions

having cost-effectiveness ratios less than US\$20,000 per QALY should be readily adopted, that those having ratios between US\$20,000 and US\$100,000 per QALY are usually provided, even though availability may be somewhat limited, and those with ratios greater than US\$100,000 per QALY have weak evidence for adoption. The CDC computer model estimate of US\$56,649 per QALY gained (CDC, 1998) suggests that clinic-based opportunistic screening is in the range of other screening procedures recommended for several other conditions (Engelgau et al, 2000).

## Summary - Why Detect Type 2 Diabetes

The following Table summaries the considerations in relation to active case detection and diagnosis for Type 2 diabetes in asymptomatic non-pregnant adults.

| <b>Criteria</b>  | <b>Met by Diabetes</b>              |
|--|-------------------------------------|
| The condition: <ul style="list-style-type: none"> <li>• Is a substantial health problem in the community to be screened</li> <li>• Has a preclinical phase during which it can be diagnosed</li> <li>• Has a substantial undiagnosed rate</li> <li>• Has an improved prognosis if treated early</li> </ul> | Yes<br>Yes<br>Yes<br>Yes            |
| Detection and management of preclinical disease results in improved outcomes   | Probable                            |
| The screening and diagnostic tests are: <ul style="list-style-type: none"> <li>• Safe</li> <li>• Acceptable to the client population</li> <li>• Easy to use</li> <li>• Relatively low cost</li> </ul>  | Yes<br>No information<br>Yes<br>Yes |
| The screening test accurately identifies a high proportion of people with early disease  | Yes                                 |
| The case detection and diagnosis procedures are cost effective   | Yes                                 |
| Potential harms <ul style="list-style-type: none"> <li>• Medical</li> <li>• Psycho-social</li> </ul>   | Uncertain<br>Uncertain              |

## Comment - Why Detect Type 2 Diabetes

Although there are no randomised trials comparing long term outcomes in screened and unscreened populations, there is now substantial evidence which, on balance, favours case detection and diagnosis for Type 2 diabetes. This evidence includes:

- Type 2 diabetes is a substantial health problem
- Type 2 diabetes has an asymptomatic preclinical phase during which it can be diagnosed
- A significant proportion of the population has undiagnosed Type 2 diabetes
- Undiagnosed Type 2 diabetes is not a benign condition
- Preliminary data suggest that detection and management of preclinical disease results in improved outcomes
- Detection of people with impaired glucose tolerance has the potential to improve outcomes and reduce the numbers progressing to Type 2 diabetes
- The case detection and diagnosis procedures are safe and cost effective
- The procedures have acceptable accuracy when applied to high risk people
- The procedures are associated with minimal harm
- The final format of a case detection and diagnosis program should also take into consideration available resources for testing and follow up and also the potential impact on the community

## Evidence Table: Is Case Detection for Type 2 Diabetes Worthwhile?

| Author   | Evidence          |                   |                |                     |                  |
|--|-------------------|-------------------|----------------|---------------------|------------------|
|  | Level of Evidence |                   | Quality Rating | Magnitude Rating    | Relevance Rating |
|  | Level             | Study Type        |                |                     |                  |
| <b>Abraira C (1995)</b><br>(Adult males – US)  | II                | RCT               | High           | High <sup>+</sup>   | High             |
| <b>Ballard DJ (1988)</b><br>(Adults - US)  | III-2             | Cohort            | High           | High <sup>+</sup>   | High             |
| <b>Barzilay JI (1999)</b><br>(Elderly – US)  | III-2             | Cohort            | High           | High <sup>+</sup>   | High             |
| <b>CDC Cost Effectiveness Study Group (1998)</b><br>(Computer model Adults – US: African American) | III-2             | Cohort            | Medium         | High <sup>+</sup>   | Low              |
| <b>Colagiuri S (2000)</b><br>(Adults – Australia)  | III-2             | Cohort            | Medium         | High <sup>+</sup>   | High             |
| <b>Croxson SCM (1994)</b><br>(Elderly – UK)  | III-2             | Cohort            | High           | High <sup>+</sup>   | High             |
| <b>DECODE Study (1999a)</b><br>(Adults – Europe)   | III-2             | Cohort            | Medium         | High <sup>+</sup>   | High             |
| <b>Easton JL (1998)</b><br>(Model Adults – Australia)  | III-2             | Cohort            | Medium         | High <sup>+</sup>   | High             |
| <b>Eschwege E (1985)</b><br>(Adults men – France)  | III-2             | Cohort            | High           | High <sup>+</sup>   | High             |
| <b>Glatthaar C (1985)</b><br>(Adults – Australia)  | III-2             | Cross-sectional   | High           | High <sup>+</sup>   | High             |
| <b>Goyder E (2000)</b><br>(Model Adults – Australia)   | III-2             | Cohort            | Medium         | High <sup>+</sup>   | High             |
| <b>Guest CS (1992)</b><br>(Adults – Euroids & Australian Aborigines)                               | III-2             | Cross-sectional   | High           | High <sup>+</sup>   | High             |
| <b>Haffner SM (1989)</b><br>(Adults - US)  | III-2             | Cross-sectional   | High           | High <sup>+</sup>   | Low              |
| <b>Harris MI (1987)</b><br>(Adults - US)   | III-2             | Cross-sectional   | High           | High <sup>+</sup>   | High             |
| <b>Harris MI (1992)</b><br>(Adults – US; Australia)  | III-2             | Cross-sectional   | High           | High <sup>+</sup>   | High             |
| <b>Harris MI (1998)</b><br>(Adults - US)   | III-3             | Cross-sectional   | High           | High <sup>+</sup>   | High             |
| <b>Jarrett RJ (1986)</b><br>(Adults males – UK)  | III-2             | Cohort            | High           | High <sup>+</sup>   | High             |
| <b>Jarrett RJ (1988)</b><br>(Adult men – UK)   | III-2             | Cohort            | High           | High <sup>+</sup>   | High             |
| <b>NHMRC (1997)</b>  | I                 | Systematic review | High           | High                | High             |
| <b>Okhubo Y (1995)</b><br>(Adults - Japan)   | II                | RCT               | Medium         | High <sup>+</sup>   | Low              |
| <b>Pan XR (1997)</b><br>(Adults - China)   | II                | RCT               | High           | High <sup>+</sup>   | Medium           |
| <b>Schneider H (1996)</b><br>(Adults – Germany)  | III-2             | Cohort            | Medium         | Medium <sup>+</sup> | High             |
| <b>UKPDS 16 (1995)</b><br>(Adults - UK)  | II                | RCT               | High           | High <sup>+</sup>   | High             |
| <b>UKPDS 33 (1998)</b><br>(Adults - UK)  | II                | RCT               | High           | High <sup>+</sup>   | High             |
| <b>Welborn TA (1997)</b><br>(Adults – Australia)   | III-2             | Cross-sectional   | High           | Low                 | High             |
| <b>Zimmet PZ (1999a)</b><br>(Adults – Australia)   | III-2             | Cross-sectional   | High           | High <sup>+</sup>   | High             |

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect. Low = no statistically significant effect

## Section 2: Case Detection and Diagnosis

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### Issue

**Who should be tested for undiagnosed Type 2 diabetes?**

### Recommendation

Testing for undiagnosed Type 2 diabetes is recommended for the following high risk individuals:

- People with impaired glucose tolerance or impaired fasting glucose;
- Aboriginal and Torres Strait Islanders aged 35 and over;
- Certain high risk non-English speaking background groups aged 35 and over (specifically Pacific Islander people, people from the Indian subcontinent or of Chinese origin);
- People aged 45 and over who have either or both of the following risk factors:
  - obesity (BMI  $\geq$  30 );
  - hypertension;
- All people with clinical cardiovascular disease (myocardial infarction, angina or stroke); and
- Women with polycystic ovary syndrome who are obese.

Individuals presenting the following risk factors are also considered to be at high risk of having undiagnosed Type 2 diabetes but further studies are required in order to evaluate any net clinical or economic benefit of testing these groups:

- Women with previous gestational diabetes;
- People aged 55 and over; and
- People aged 45 and over who have a first degree relative with Type 2 diabetes.

An economic analysis should be undertaken to evaluate the benefits of screening for undiagnosed Type 2 diabetes in women with a previous history of gestational diabetes, people aged 55 and over, and for people aged 45 and over who have a first degree relative with Type 2 diabetes.

### Evidence Statements

- The majority of people with undiagnosed Type 2 diabetes have readily identifiable risk factors  
*Evidence Level III-2*
- People in the following groups are at increased risk of developing Type 2 diabetes:
  - Impaired glucose tolerance - *Evidence Level III-2*
  - Impaired fasting glucose - *Evidence Level III-2*
  - History of gestational diabetes – *Evidence Level III-2*
- People in the following groups are at increased risk of having undiagnosed Type 2 diabetes:
  - Aged 55 and over – *Evidence Level III-2*
  - Aboriginal and Torres Strait Islanders aged 35 and over – *Evidence Level III-2*
  - Pacific Islander peoples, people from the Indian subcontinent and Chinese people aged 35 and over – *Evidence Level III-2*
  - Aged 45 and over with one or more of the following risk factors:
    - Obesity (BMI  $\geq 30$ ) – *Evidence Level III-2*
    - first degree relative with Type 2 diabetes – *Evidence Level III-2*
    - hypertension – *Evidence Level III-2*
  - Those with clinical cardiovascular disease – *Evidence Level III-2*
  - Obese women with polycystic ovary syndrome – *Evidence Level III-2*

## Background – Who Should be Tested

The overall prevalence of Type 2 diabetes in Australia is not high enough to justify universal testing of the whole population. The previous section summarised the evidence in favour of opportunistic testing for undiagnosed Type 2 diabetes. This section addresses the question of risk factors which identify a subgroup of the population at increased risk of undiagnosed Type 2 diabetes.

Many studies have examined the relationship between risk factors and Type 2 diabetes. In developing these clinical guidelines, the focus has been on identifying risk factors which can be recognised by health professionals, particularly general practitioners, during a routine consultation or which can be expected to be routinely and readily measured in everyday practice.

In reviewing the literature on potential risk factors, emphasis has been placed on studies which prospectively evaluated risk factors in the development of diabetes or which reported associations of risk factors at the time of diagnosis of previously undiagnosed Type 2 diabetes. Another consideration in the identification of clinically useful risk factors is that many studies have reported relative risk (RR) data which do not specify definitive cut off levels for a continuous variable and therefore do not allow translation of this information for routine clinical use. For example an association of elevated triglyceride levels and the development of Type 2 diabetes has been reported by some, but not all, studies. The reporting of RR as a comparison of upper and lower quintiles without stating actual levels, does not allow the identification of a particular triglyceride level above which risk may be increased and which could be used in the identification of an at risk individual who should then be tested for undiagnosed Type 2 diabetes.

International diabetes organisations have published recommendations for identifying individuals at risk who should be tested for Type 2 diabetes (Canadian Medical Association, 1998; ADA, 2000). These risk factor statements represent current consensus and have not been developed through a systematic evidence based process. Therefore, there are no universally agreed criteria for developing evidence based recommendations for case detection strategies for undiagnosed Type 2 diabetes.

The basic criterion adopted in the preparation of these guidelines for identifying risk factors for active case detection of undiagnosed Type 2 diabetes is that a single risk factor or a combination of risk factors should detect a prevalence of undiagnosed Type 2 diabetes of 5% i.e. identify groups of individuals with a 1 in 20 chance of having undiagnosed Type 2 diabetes. A prevalence of undiagnosed diabetes of 5% was also used by Herman et al (1995) to identify risk factors for undiagnosed Type 2 diabetes.

The decision to adopt this criterion in formulating these guidelines does not preclude the testing of population groups with a lower prevalence of undiagnosed Type 2 diabetes depending on local circumstances.

Identification of people at risk of having undiagnosed Type 2 diabetes or at risk of the future development of Type 2 diabetes is the initial step of a staged process of case detection and diagnosis. The second step in the at risk individual is measurement of plasma glucose, followed by an oral glucose tolerance test if glucose tolerance status is still undecided, and finally confirmation of the diagnosis. A major aim of this staged approach is to minimise the number of individuals who would need to have an oral glucose tolerance test.

## Evidence – Who Should be Tested

**The majority of people with undiagnosed Type 2 diabetes have readily identifiable risk factors.**

Most people with undiagnosed Type 2 diabetes have easily identifiable risk factors and is the basis for targeted testing of high risk groups to identify most cases of undiagnosed Type 2 diabetes.

Cowie et al (1994) reported data from 19 680 people age 18 years or more without a medical history of diabetes who participated in the 1989 National Health Interview Survey. Seventy eight percent had at least one risk factor for Type 2 diabetes and 22.9% had 3 or more risk factors. Prevalence of diabetes was related to risk factors using data from NHANES II (Harris et al, 1987). Prevalence of undiagnosed diabetes was 11.7% in people with 3 risk factors (older age, family history and obese) compared with 0.4% for people without these risk factors.

**People in the following groups are at increased risk of developing Type 2 diabetes:**

### ***1. Impaired Glucose Tolerance (IGT)***

IGT is prevalent in Caucasian populations with recent reports showing overall rates of the order of 10% (Harris et al, 1987; Heine et al, 1996). The prevalence of IGT increases with increasing age. The NHANES III study (Harris et al, 1998) reported a prevalence of IGT of 11.1% for people aged 40-49 and 20.9% in the 60-74 age group.

A number of population based studies from various parts of the world have calculated the risk of progression to Type 2 diabetes from IGT, including two recent reviews (Alberti 1996; Edelstein et al, 1997). Data are available from many different population studies from Europe, USA, India, Africa and the Pacific Islands. Table 1 summarises the data from studies which included an assessment using an oral glucose tolerance test (OGTT) interpreted according to WHO 1985 criteria (WHO, 1985) to define and follow up people with IGT. The annual rate of development of Type 2 diabetes in people with IGT ranged from 1.8 to 12.6%. The average annual rate in Caucasians was 4.7%, 7.7% in indigenous populations and 6.2% in people from the Pacific Islands. These rates compare with average annual incidence rates for Type 2 diabetes of 0.7% in Caucasian people with normal glucose tolerance.

Pettitt et al (1996) have compared the rates of progression of IGT to diabetes in Pima Indian women who were, or were not pregnant when IGT was first diagnosed. Interestingly, the annual incidence of diabetes over a 10 year period was higher in women with IGT diagnosed when not pregnant (9.2% v 4.5%).

**Table 1: Annual rates of progression from IGT to Type 2 diabetes**

| Population                 | Age of population studied | Annual progression to Type 2 diabetes |       | Reference              |
|----------------------------|---------------------------|---------------------------------------|-------|------------------------|
|                            |                           | IGT                                   | NGT # |                        |
| <b>Caucasians</b>          |                           |                                       |       |                        |
| Finland                    | 65-84                     | 2.3%                                  | 0.8%  | Stengard, 1993         |
| Finland                    | 65-74                     | 6.7%                                  | 0.9%  | Mykkanen, 1993         |
| Hoorn Study, Netherlands   | 50-74                     | 11.3%                                 | -     | Nijpels, 1997          |
| Malta                      | 35-69                     | 5.1%                                  | 0.7%  | Schranz, 1989          |
| Paris Prospective Study    | 50-60                     | 1.8%                                  | 0.9%  | Charles, 1991          |
| USA - Baltimore Study      | 17-92                     | 3.6%                                  | -     | Edelstein review, 1997 |
| - Rancho Bernardo Study    | 50-89                     | 4.0%                                  | -     | Edelstein review, 1997 |
| - San Antonio Heart Study* | 25-64                     | 2.8%                                  | -     | Edelstein review, 1997 |
| - San Luis Valley Study*   | 20-74                     | 4.8%                                  | 0.3%  | Edelstein review, 1997 |
| China, Da Qing             | 25-74                     | 11.3                                  | -     | Pan, 1997              |
| <b>Indian Subcontinent</b> |                           |                                       |       |                        |
| Chennai                    | 35-72                     | 8.4%                                  |       | Ramachandran, 1986     |
| South Africa               | 47 (mean)                 | 12.6%                                 |       | Motala, 1993           |
| Tanzania                   | 25-65                     | 2.0%                                  |       | Swai, 1990             |
| Mauritius                  | 25-74                     | 3.8%                                  | 0.9%  | Shaw, 1999             |
| Mexican Americans          |                           |                                       |       |                        |
| - San Antonio Heart Study  | 25-64                     | 4.8%                                  | -     | Edelstein review, 1997 |
| - San Luis Valley Study    | 20-74                     | 9.6%                                  | 0.8%  | Edelstein review, 1997 |
| <b>Pacific Islands</b>     |                           |                                       |       |                        |
| Nauru                      | 12-75                     | 6.3%                                  | 1.2%  | Edelstein review, 1997 |
| Niue                       | Not stated                | 6.0%                                  | -     | Tukuitonga, 1990       |
| Pima Indians               | 20-90                     | 8.7%                                  | 1.0%  | Edelstein review, 1997 |
| Taiwan, Kinman Islands     | > 30                      | 8.8%                                  | 1.8%  | Chou, 1998             |

\* Non-Hispanic Whites

# NGT – normal glucose tolerance

## 2. Impaired Fasting Glucose (IFG)

IFG is a relatively new category of glucose intolerance i.e. fasting plasma glucose between 6.1 and 6.9 mmol/l and defines a smaller subgroup of the non-diabetic population compared with IGT. For example the results of the AusDiab study show a prevalence of IGT of 10.6% and of IFG of 6.5% (Zimmet et al, 2000). A small number of studies have reported the annual conversion rate from IFG to Type 2 diabetes. In Caucasian populations Charles et al (1991) reported an annual progression rate of 1% and Vaccaro et al (1999) reported rates of 2.2% while rates of 5.8% were reported from Mauritius (Shaw et al, 1999a).

## 3. Gestational diabetes (GDM)

Many studies have reported that women with a previous history of gestational diabetes are at increased risk of developing Type 2 diabetes (O'Sullivan, 1989). All studies have consistently confirmed this increased risk but differing methodologies make the comparison of studies, and therefore the quantitation of the effect, difficult. Methodological issues include: differences in the diagnostic tests and criteria for diagnosing GDM in the index pregnancy and for diagnosing Type 2 diabetes postpartum, non-representative populations of women who undergo postpartum testing for Type 2 diabetes, variable lengths of follow up, geographic and ethnic differences and the lack of a control group in most studies (Damm et al, 1992). In addition studies have usually been clinic rather than population based.

Studies which have used an OGTT to diagnose diabetes postpartum and which have included a control group are summarised in Table 2. From these studies, the mean annual incidence of diabetes in predominantly Caucasian women with previous GDM is 1.4%, 14 times greater than in the control group (0.1%). McGuire et al (1996) examined the records of women with 2 or more births between 1984 and 1991 and reported an odds ratio of 57.3 for a self reported diagnosis of new diabetes in women with previous GDM compared to women without GDM

in the previous pregnancy. The risk of developing Type 2 diabetes continues for many years after the index pregnancy (O’Sullivan, 1989). The Hanson et al (1996) study cited in Table 2 is an extension of the Persson et al study (1991) and indicates similar rates of progression for the first and second 3 year periods.

**Table 2: Risk of Type 2 diabetes in women with previous gestational diabetes compared with a control group**

| Reference                          | Number of women with GDM | DM diagnosis (post-partum) | Follow-up period (y) | Crude annual incidence (%) of Type 2 diabetes |          |
|------------------------------------|--------------------------|----------------------------|----------------------|---|----------|
|                                    |                          |                            |                      | GDM   | Controls |
| Damm, 1989 (Denmark)               | 241                      | 75g OGTT                   | 6 median             | 2.3%  | 0%       |
| Hanson, 1996 (Sweden)              | 97                       | 75g OGTT                   | 6                    | 1.1%  | 0%       |
| Henry & Beischer, 1991 (Australia) | 881                      | 75 g OGTT                  | 1to 17               | 1.3%*   | 0.1%*    |
| O’Sullivan, 1989 (US)              | 615                      | 100g OGTT                  | 22-28                | 1.4%  | 0.2%     |
| Persson, 1991 (Sweden)             | 145                      | 75g OGTT                   | 3-4                  | 1.0%  | 0%       |

\* Neither the annual rate nor the mean or median follow-up are given in this study. Numbers representing calculated figures are only estimates.

The rates of development of Type 2 diabetes in women with previous GDM in populations with higher prevalence rates of diabetes are even greater (Table 3), although only one of these studies included a comparative control group (Benjamin et al, 1993) and reported an annual incidence of development of Type 2 diabetes of 1.2% in non-GDM affected women compared with 6.3% following a GDM pregnancy.

Unfortunately, there is no data on rates of progression of Aboriginal or Torres Strait Islander women affected by GDM or ethnic populations commonly represented in Australia.

**Table 3: Risk of Type 2 diabetes in women with previous gestational diabetes in populations with a high prevalence of diabetes.**

| Reference                                  | Number of women with GDM | DM diagnosis (post-partum) | Follow-up period (y) | Annual DM incidence (%)                    |
|--|--------------------------|----------------------------|----------------------|--|
| Benjamin, 1993 (Zuni Indian, US)           | 47                       | 75g OGTT                   | 5 (mean)             | 6.3%                                       |
| Metzger, 1993 (31% black, 35% hispanic US) | 274                      | 100g OGTT                  | 5                    | 25% for 1 <sup>st</sup> year and then 5-6% |
| Peters, 1996 (Latino, US)                  | 666                      | 75g OGTT                   | Up to 8              | 11.9%                                      |
| Steinhart, 1997 (Navajo Indians, US)       | 88                       | 75g OGTT                   | Up to 11             | 4.8%                                       |

## **People in the following groups are at increased risk of having undiagnosed Type 2 diabetes:**

### ***Age as a risk factor***

The purpose of considering age as a risk factor is to determine an age cut-off above which it is either an independent risk factor or a risk factor in combination with other recognised risk factor(s) to identify people who should be tested for undiagnosed Type 2 diabetes. The objective of this aspect of the guideline is to identify risk factors which are associated with a 5% prevalence of undiagnosed Type 2 diabetes. Therefore, an age cut-off which would meet this objective would either:

- have a prevalence of undiagnosed diabetes of 5% or
- have a prevalence of undiagnosed diabetes of 2.5% combined with a risk factor (eg family history) which doubles the chance of having undiagnosed diabetes.

### ***1. Caucasian populations***

The prevalence of Type 2 diabetes increases with age and this applies to both diagnosed and undiagnosed diabetes. The reported prevalence rates of undiagnosed Type 2 diabetes for various age groups in Caucasian populations is shown in Table 4. These data demonstrate that prevalence rates differ in different parts of the world. These differences may represent genuine differences or may reflect differing methodologies for diagnosing diabetes or population characteristics.

AusDiab, the definitive Australian population study using a census-based stratified sample and OGTT testing has recently provided data on 6 382 people aged 25 or older who have completed testing in Victoria, Western Australia, New South Wales and Tasmania (Zimmet et al, 2000). Data are also available from 5 previously published Australian studies (Glatthaar et al, 1985; Welborn et al, 1989; Guest et al, 1992; Welborn et al, 1997; Mitchell P et al, 1998). AusDiab shows rates of undiagnosed Type 2 diabetes of 5% in people aged 55 and above (Table 4).

From population studies in other parts of the world, rates for undiagnosed Type 2 diabetes have been higher in the USA than in Europe and the UK. The NHANES II and III studies (Harris et al, 1987; Harris et al, 1998) showed 5% prevalence of undiagnosed Type 2 diabetes in people aged 55-64 and 50-59 respectively. In contrast, in European studies this level was reached only at older ages of - 60-69 (Simmons et al, 1991; Mooy et al, 1995),  $\geq 65$  (Costa et al 1998), 65-74 (Garancini et al, 1995; Stolk et al, 1997), and  $\geq 70$  (Forrest et al, 1986). In some studies this level was not reached even up to age 75 (Yudkin et al, 1993) (Table 4).

These results lead to a recommendation that age as an independent risk factor for testing for undiagnosed Type 2 diabetes should be set at 55 years and over for the general Australian population. Setting an upper age limit is difficult because there are no data to indicate an age limit at which benefits might be expected from treating previously undiagnosed Type 2 diabetes. It is however considered that benefits from the detection of asymptomatic Type 2 diabetes are unlikely in people over 80 years.

As reviewed elsewhere in this section, obesity, family history and hypertension double the chance of having undiagnosed Type 2 diabetes. Therefore, an age cut-off which identifies a 2.5% prevalence of undiagnosed diabetes could be combined with these other risk factors to reach the target objective of identifying groups of people with a 5% prevalence of undiagnosed Type 2 diabetes.

**Table 4: Age-specific prevalence of undiagnosed Type 2 diabetes in Caucasian populations**

| Reference         | Population studied   | Diagnostic criteria   | Prevalence ND Type 2 diabetes  |       |       |       |
|-------------------|--|---|--|-------|-------|-------|
| Costa, 1998       | Catalonia Spain<br>3839 people, age 30-89  | OGTT  | 34-45  | 1.3%; | 45-54 | 3.2%  |
|                   |  |   | 55-64  | 4.3%; | ≥ 65  | 7.9%  |
| Forrest, 1986     | Islington Diabetes Survey<br>Age > 40<br>1040 people<br>75% northern European                        | 2h post load capillary blood glucose after 75 g glucose taken at home | 40-49  |       | Men   | Women |
|                   |  |   | 50-59  |       | -     | 1.0   |
|                   |  |   | 60-69  |       | 3.6   | 1.9   |
|                   |  |   | 70-79  |       | 3.1   | 1.6   |
|                   |  |   |  |       | 5.6   | 5.1   |
| Garancini, 1995   | Cremona, Italy<br>2618 people; Age > 44  | OGTT  | 45-54  | 1.3%; | 1.8%  |       |
|                   |  |   | 65-74  | 5.0%; | > 75  | 5.9%  |
| Glatthaar, 1985   | Busselton, Australia<br>3197 males and females<br>1981 survey; ≥ 25                                  | OGTT (glucose consumed at home)                                       | 35-44  | 0.6%; | 45-54 | 0.4%  |
|                   |  |   | 55-64  | 0.6%; | 65-74 | 3.3%  |
|                   |  |   | ≥ 75   | 5.1%  |       |       |
| Guest, 1992#      | Victorian Country towns, Australia<br>553 Europids<br>Age > 15                                       | OGTT<br>KDM from medical records                                      | 35-44  | 1.5%  |       |       |
|                   |  |   | 45-54  | 3.0%  |       |       |
|                   |  |   | 55-64  | 3.0%  |       |       |
|                   |  |   | ≥ 65   | 20%   |       |       |
| Harris, 1987      | NHANES II, US<br>1976-1980<br>3772 tested with OGTT<br>Age 20-74                                     | OGTT<br>(Results in Table for white population)                       | 20-44  |       | Men   | Women |
|                   |  |   | 45-54  |       | 1.0%  | 0.7%  |
|                   |  |   | 55-64  |       | 4.2%  | 4.0%  |
|                   |  |   | 65-74  |       | 6.0%  | 6.5%  |
|                   |  |   |  |       | 8.9%  | 9.0%  |
| Harris, 1998      | NHANES III, US<br>1988-1994<br>2844 aged 40-74 had h OGTT  | OGTT  | 40-49  | 1.9%  |       |       |
|                   |  |   | 50-59  | 5.5%  |       |       |
|                   |  |   | 60-74  | 11.0% |       |       |
| Mitchell, P, 1998 | Blue Mountains, Australia<br>1992-1994<br>3029 non-diabetic people<br>Age > 49                       | FPG<br>ADA criteria   | < 60   | 1.8%  |       |       |
|                   |  |   | 60-69  | 2.4%  |       |       |
|                   |  |   | 70-79  | 3.5%  |       |       |
|                   |  |   | > 80   | 5.0%  |       |       |
| Mooy, 1995        | Hoorn study, Netherlands<br>2484 people<br>Age 50-75   | OGTT  | Overall  | 4.8%  | Men   | Women |
|                   |  |   | 50-54  |       | 1.4%  | 1.0%  |
|                   |  |   | 55-59  |       | 5.7%  | 2.1%  |
|                   |  |   | 60-64  |       | 4.2%  | 6.5%  |
|                   |  |   | 65-69  |       | 5.5%  | 5.5%  |
|                   |  |   | 70-74  |       | 9.0%  | 9.9%  |
| Simmons, 1991 #   | Coventry Diabetes Study – 1986-89; 3529 Europids, 3693 Asians; Age > 20; Asian = Indian subcontinent | OGTT<br>(after screening with RcapBG)                                 | 5% ND:<br>40-49 year age group for Asians<br>60-69 year group for Europids |       |       |       |
| Stolk, 1997       | Rotterdam study, Netherlands<br>1990-1993<br>6618 males and females<br>Age ≥ 55                      | OGTT<br>Non-fasting   | 55-64  |       | Men   | Women |
|                   |  |   | 65-74  |       | 0.9%  | 3.2%  |
|                   |  |   | ≥ 75   |       | 6.0%  | 5.6%  |
|                   |  |   |  |       | 9.4%  | 10.1% |
| Tuomilehto, 1991  | FINMONICA, Finland, 1987<br>2718 people; age 45-64   | OGTT  | 45-54  | 0.6%  |       |       |
|                   |  |   | 55-64  | 2.0%  |       |       |
| Welborn, 1989     | NHF Risk factor Prevalence Survey, Australia, 1983<br>10083 participants; age 25-64                  | FPG ≥ 7.8   | 35-44  | 0.2%  |       |       |
|                   |  |   | 45-54  | 0.6%  |       |       |
|                   |  |   | 55-64  | 1.0%  |       |       |
| Welborn, 1997     | Australian Diabetes Screening Study, 1994/1995; age > 40<br>23200 had RPG<br>8648 had OGTT           | Screened for risk factors<br>If RPG > 5.5<br>Then OGTT                | 40-49  | 0.5%  |       |       |
|                   |  |   | 50-59  | 1.6%  |       |       |
|                   |  |   | 60-69  | 2.4%  |       |       |
|                   |  |   | > 70   | 3.3%  |       |       |
| Yudkin, 1993      | North London, UK<br>1919 people tested<br>Age 40-75  | OGTT  | 45-54  |       | Men   | Women |
|                   |  |   | 55-64  |       | 1.4%  | 1.8%  |
|                   |  |   | 60-64  |       | 3.8%  | 1.4%  |
|                   |  |   | 65-75  |       | 5.6%  | 2.8%  |
|                   |  |   |  |       | 4.3%  | 3.4%  |
| Zimmet, 2000      | Australia (Vic, WA, NSW, Tas)<br>6382 people tested<br>Age ≥ 25                                      | OGTT  | 40-44  |       | Men   | Women |
|                   |  |   | 45-49  |       | 2.4%  | 0.6%  |
|                   |  |   | 50-54  |       | 4.3%  | 1.7%  |
|                   |  |   | 55-59  |       | 4.6%  | 3.4%  |
|                   |  |   | 60-64  |       | 5.3%  | 4.9%  |
|                   |  |   |  |       | 9.5%  | 4.1%  |

ND = newly diagnosed; KDM = known diabetes mellitus; ADA = American Diabetes Association  
RPG=random plasma glucose; FPG=fasting plasma glucose; OGTT=75g glucose and WHO criteria unless indicated  
# Age specific data extrapolated from information contained in the paper

AusDiab shows an age cut-off of 45-49 when the prevalence of undiagnosed Type 2 diabetes reaches 2.5% (Table 4, Zimmet et al, 2000). The age cut-off for a 2.5% prevalence of undiagnosed diabetes in other studies is 45-54 (Harris et al, 1987; Guest et al, 1992; Costa et al, 1998), 50-59 (Forrest et al, 1986), 55-59 (Mooy et al, 1995), 55-64 (Tuomilehto et al, 1991; Stolk et al, 1997), 60-69 (Welborn et al, 1997; Mitchell et al, 1998), and 65-74 (Glatthaar et al, 1985; Yudkin et al, 1993). Combining these Australian, USA, European and UK data (Table 4) indicate that people 45 years and over have a prevalence of undiagnosed diabetes of 2.5% and that this age can be combined with the other risk factors of obesity, family history and hypertension.

## **2. *Aboriginal and Torres Strait Islanders***

De Courten et al (1998) have performed a systematic review of data on Type 2 diabetes in Australia's indigenous population of Aboriginal and Torres Strait Islanders. While methodological issues make direct comparisons between studies difficult and although reported prevalence rates have varied, all studies have documented an increased prevalence of Type 2 diabetes compared with reported rates in non-indigenous Australians.

Overall prevalence rates of Type 2 diabetes of 10-30% are commonly reported. Where direct comparisons have been made with non-indigenous Australians (Guest et al, 1992), age standardised rates are 4 times higher in Aboriginal and Torres Strait Islanders. A feature of Type 2 diabetes in Aboriginal and Torres Strait Islanders is its earlier age of diagnosis. Braun et al (1996) reported rates of undiagnosed diabetes of 2.7% in young Aborigines (mean age 18.3 years) from the Kimberley Region of Western Australia. Daniel et al (1999) recently reported the first incidence study of diabetes in Aboriginal people from Central Australia followed for 7-8 years. The annual incidence of Type 2 diabetes was 2% and was substantially modified by weight reaching 3.8% in people aged 35 and over with a BMI of 33 or more. These data have also been analysed according to homelands status of individuals and suggest that people who live in homeland communities have lower rates of diabetes (McDermott et al, 1998).

Most reports have not distinguished between known diabetes and newly diagnosed diabetes and few have reported age-specific rates of undiagnosed diabetes. Table 5 provides a summary of studies which report or contain sufficient information to allow a calculation of age related prevalence rates of newly diagnosed Type 2 diabetes in Aboriginal and Torres Strait Islanders.

The results of these studies indicate that undiagnosed Type 2 diabetes is prevalent in Aboriginal and Torres Strait Islanders and that this increased prevalence occurs at a younger age than in non-indigenous people. All studies have shown a prevalence of undiagnosed Type 2 diabetes of 5% in people 35 years or older and 2 studies have shown that this rate may be reached in even younger individuals (Bastian et al, 1979; Cameron et al, 1986). Applying all these data to the objective of identifying a 5% prevalence of undiagnosed Type 2 diabetes, Aboriginal and Torres Strait Islanders 35 years of age and over should be tested. The data also suggest that in some communities the age range for testing should be even lower.

**Table 5: Age-specific prevalence of undiagnosed Type 2 diabetes in Aboriginal and Torres Strait Islander populations**

| Reference        | Population studied  | Diagnostic criteria  | Prevalence ND Type 2 diabetes  |
|------------------|---|--|--|
| Bastian, 1979    | West Kimberley, Western Australia<br>1977<br>248 full blooded tribal Aborigines                   | Screening with non-fasting 50g dextrose load if 1 hour BG > 12.5 had 50g OGTT , DM if 2 h >8.4 | Overall: 10% M 14% F<br>Men Women<br>30-39 10% 20%<br>40-49 11.5% 25%<br>50-59 26% 26%   |
| Cameron, 1986    | Bourke and Enngonia, NSW, Australia<br>294 Aboriginal people<br>Age > 20                          | OGTT if not KDM after initial random blood and if HbA <sub>1c</sub> elevated or BG ≥ 8         | Overall: 6.7% M 5.6% F<br>Men Women<br>25-34 8.7% 9.5%<br>35-44 6.1% 3.6%<br>45-54 12.5% 0%<br>55-64 15.4% 0%<br>≥ 65 0% 28.6% |
| Colagiuri, 1999a | Urban Sydney, Australia<br>203 non-diabetic Aboriginal people<br>Age > 15                         | OGTT   | Overall: 7.4%<br>35-44 5.9%<br>45-54 5.5%<br>55-64 21%   |
| Guest, 1992      | Victorian Country towns, Australia<br>306 Aboriginal people<br>Age > 15                           | OGTT<br>KDM from medical records<br>KDM to ND 2:1  | Overall 2.2%<br>25-34 3.0%<br>35-44 10.0%<br>≥ 45 16.0%  |
| O’Dea, 1982      | Kimberly Region, Western Australia, Survey in 1979<br>67 non-diabetic Aboriginal people, Age ≥ 15 | OGTT interpreted using NDDG criteria   | 15-35 0%<br>> 35 9.4%  |
| O’Dea, 1988 #    | Kimberly Region, Western Australia, Survey 1983-4<br>148 Aboriginal people<br>Age ≥ 15            | OGTT WHO 1980  | Men Women<br>15-35 2.8% 0%<br>>35 7.4% 9.5%  |
| O’Dea 1990 #     | North western Northern Territory, 122 people<br>Age > 17  | OGTT WHO 1980  | Overall: 11.5%<br>Men Women<br>18-35 6.1% 0%<br>>35 23.5% 22.9%  |

ND = newly diagnosed; KDM = known diabetes mellitus; ADA = American Diabetes Association  
RPG=random plasma glucose; FPG=fasting plasma glucose; OGTT=75g glucose and WHO criteria unless indicated  
# Derived from results in paper or assumed reported diabetes was all newly diagnosed Type 2 diabetes

### 3. People from a non-english speaking background

There is a wealth of data confirming the marked increase in diabetes prevalence in non-Caucasian populations in many parts of the world which has been associated with changing from a traditional to a western lifestyle.

Australia is a nation of immigrants and is reputed to be one of the most multi-cultural nations in the world. The overseas born population accounted for 23% of Australia’s total population in 1996 (ABS, 1997c). Ethnicity is a well documented risk factor for diabetes and many of the ethnic groups with high prevalence rates of diabetes are represented in Australia. Type 2 diabetes is not only prevalent in some ethnic groups but also occurs at a younger age. The purpose of this part of the review was to identify ethnic groups represented in Australia which have a high prevalence of Type 2 diabetes and the age cut-off above which the prevalence of undiagnosed Type 2 diabetes reaches 5%.

Information is available on prevalence rates for some of the ethnic groups more commonly represented in Australia which include people from Europe, Chinese origin, the Indian subcontinent, Pacific Islander people and those of Arabic background. As with other aspects of this guideline, studies have varied in their methodology and in their reporting of age-specific rates of newly diagnosed Type 2 diabetes. Table 6 summarises studies which contain relevant data on this topic. Table 7 further summarises these data for age of 5% prevalence of undiagnosed Type 2 diabetes for the different ethnic groups. European populations have been

considered previously as part of the overall Caucasian population and the age at which the 5% undiagnosed prevalence rate is reached is 65 years and over.

People of Chinese, Indian and Pacific Islander background have a higher prevalence of diabetes and the diabetes which also develops at a younger age. Some, but not all, Arabic populations have a higher prevalence of diabetes and the available literature is limited as to whether this increase generally commences at a younger age.

Pacific Islander people have among the highest rates of Type 2 diabetes in the world. The recent data from both Nauru and Tonga demonstrate that the age cut-off for 5% undiagnosed Type 2 diabetes is 25-30 years (Colagiuri, 1999b; Zimmet, 1999b). People from the Indian sub-continent have been consistently shown to reach a 5% prevalence of undiagnosed diabetes at ages from 30-40 years (Dowse et al, 1990; Simmons et al, 1991; Ramachandran et al, 1992; Omar et al, 1994; Shera et al, 1995; Tan et al, 1999). The studies on Chinese populations living outside mainland China also consistently show a high prevalence of diabetes. However, the age for a 5% prevalence of undiagnosed diabetes has varied between 35 and 50 years of age (Dowse et al, 1990; Cockram et al, 1993; Unwin et al, 1997; Lu et al, 1998; Tan et al, 1999). Combining the studies in Chinese people suggests a cut-off in the region of 40 years of age for a prevalence of undiagnosed Type 2 diabetes of 5%. Only 2 recent studies were identified which provided age-specific data on prevalence rates in Arabic populations. These studies showed widely different rates of undiagnosed diabetes (7.8% in Iran [Amini et al, 1997] and 14% in the Sultanate of Oman [Asfour et al, 1995]) and the age cut-off for reaching 5% undiagnosed Type 2 diabetes ranged from 40-49 in the Sultanate of Oman (Asfour et al, 1995) to 60-69 in Iran (Amini et al, 1997).

Clearly, certain ethnic populations represented in Australia are at increased risk of having undiagnosed Type 2 diabetes at a younger age than occurs in Caucasian populations. The evidence suggests a single recommendation that non-English speaking background people from the Pacific Islander people, Indian subcontinent and of Chinese origin should be considered for testing for undiagnosed Type 2 diabetes from age 35 years and over.

**Table 6: Age cut-off for prevalence of undiagnosed Type 2 diabetes of 5% for various non-English speaking background populations**

| Reference               | Population studied  | Diagnostic criteria                            | Prevalence of ND Type 2 diabetes                                   |        |         |       |
|-------------------------|---|--|--|--------|---------|-------|
| Amini, 1997 #           | Isfahan, Iran; 1993<br>3910 people; age > 40  | OGTT if FPG >6.4                               | 40-49  | 2.8%;  | 50-59   | 3.2   |
|                         |   |  | 60-69  | 5.0%;  | ≥ 70    | 3.9%  |
| Asfour, 1995 #          | Sultanate of Oman<br>Survey 1991<br>5096 people; age ≥ 20   | OGTT<br>KDM=<br>Medication or insulin          | 20-29  | 0.7%;  | 30-39   | 2.5%  |
|                         |   |  | 40-49  | 7.9%;  | 50-59   | 10%   |
|                         |   |  | 60-69  | 10.8%; | 70-89   | 31%   |
| Cockram, 1993 #         | Hong Kong<br>1513 Chinese<br>Age –18-6  | OGTT<br>KDM=<br>Medication or insulin          | 20-29  | 0.6%;  | 30-39   | 2.3%  |
|                         |   |  | 40-49  | 3.3%;  | 50-59   | 7.8%  |
|                         |   |  | 60-65  | 9.5%   |         |       |
| Colagiuri, 1999b        | Tonga<br>608 ND people<br>Age > 15  | FBG – 75g OGTT if<br>FBG > 5.0                 | 30-34  | 6.7%;  | 35-39   | 8.2%  |
|                         |   |  | 40-44  | 16.4%; | 45-54   | 13.6% |
|                         |   |  | 55-59  | 15.4%; | 60-64   | 19.2% |
|                         |   |  | 65+  | 22.0%  |         |       |
| Dowse, 1990             | Mauritius, Survey 1987,<br>5080 people; age 25-74<br>Indian, Creole, Chinese  | OGTT if FPG < 7.8                              | 25-34  | 2.6%;  | 35-44   | 6.5%  |
|                         |   |  | 45-54  | 10.5%; | 55-64   | 11.4% |
|                         |   |  | 65-74  | 16.1%  |         |       |
| Lu, 1998                | Tainan, Southern<br>Taiwan, 1995<br>1638 people, age ≥20  | OGTT unless history<br>of KDM                  | 20-29  | 1.2%;  | 30-39   | 2.0%  |
|                         |   |  | 40-49  | 6.5%;  | 50-59   | 13.5% |
|                         |   |  | 60-69  | 25.8%; | >70     | 26.9% |
| Omar, 1994 #            | Durban, South Africa<br>2479 Indian people<br>Age > 15  | All had OGTT<br>Including KDM                  | ≥ 35 5% ND   |        |         |       |
| Ramachandran,<br>1992 # | Madras, India; Asian<br>Indians, 1988-9, age ≥20,<br>900 urban, 1038 rural  | OGTT using meter<br>Measured<br>Capillary BG   | 20-34  | 1.8%   |         |       |
|                         |   |  | 35-54  | 7.0%   |         |       |
|                         |   |  | > 55   | 6.9%   |         |       |
| Shera, 1995             | Shikapur, Pakistan<br>Rural town, 1994<br>967 people, age ≥ 25  | OGTT unless KDM                                | 25-34  | 1.7%;  | 35-44   | 9.1%  |
|                         |   |  | 45-54  | 8.5%;  | 55-64   | 11.5% |
|                         |   |  | 65-74  | 8.3%   |         |       |
| Simmons, 1991 #         | Coventry, UK, 1986-9<br>3529 Europids<br>3693 Indian<br>subcontinent, Age >20   | OGTT if RcapBG > 6<br>nonfasting or >5 fasting | 5% ND:<br>40-49 year age group Asians<br>60-69 year group Europids |        |         |       |
| Tan, 1999 #             | Singapore National<br>Health Survey, 1992<br>3568 people Chinese<br>60%, Malays 20%<br>Asian Indians 20%<br>Age 18-69 | OGTT except if had<br>KDM                      | Chinese Malay Indian   |        |         |       |
|                         |   |  | 18-29  | 0.5%   | 0.6%    | 0.8%  |
|                         |   |  | 30-39  | 1.9%   | 3.5%    | 5.1%  |
|                         |   |  | 40-49  | 7.0%   | 8.7%    | 11.8% |
|                         |   |  | 50-59  | 10.2%  | 15.0%   | 14.6% |
|                         |   |  | 60-69  | 17.1%  | 17.4%   | 19.2% |
| Unwin, 1997             | Newcastle, UK<br>1991-4, age 25-64<br>375 Chinese people<br>610 Europids  | OGTT or KDM                                    | Chinese  |        |         |       |
|                         |   |  | 25-34  | 0%;    | 35-44   | 4.3%  |
|                         |   |  | 45-54  | 7.0%;  | 55-64   | 19.6% |
| Zimmet, 1999b           | Nauru<br>1994<br>1442 people<br>Age ≥ 25  | OGTT or KDM                                    |  | Males  | Females |       |
|                         |   |  | 25-34  | 14.5%  | 11.1%   |       |
|                         |   |  | 35-44  | 21.7%  | 17.7%   |       |
|                         |   |  | 45-54  | 25.0%  | 20.9%   |       |
|                         |   |  | 55-64  | 11.1%  | 22.4%   |       |
|                         |   |  | 65-74  | 4.5%   | 29.6%   |       |
|                         |   |  | 75-84  | 0%     | 11.1%   |       |

ND = newly diagnosed; KDM = known diabetes mellitus; ADA = American Diabetes Association

RPG=random plasma glucose; FPG=fasting plasma glucose; OGTT=75g glucose and WHO criteria unless indicated

# Derived from results in paper or assumed reported diabetes was all newly diagnosed Type 2 diabetes

**Table 7: Age cut-off for prevalence of undiagnosed Type 2 diabetes of 5% for various non-English speaking background populations**

| Population   | Reference  | Age for prevalence undiagnosed diabetes > 5%     |
|--|--|--|
| <b>Chinese</b><br>Hong Kong<br>Mauritius<br>Singapore<br>Taiwan<br>UK                                  | Cockram<br>Dowse<br>Tan<br>Lu<br>Unwin                   | > 50<br>35-44<br>> 40<br>40-49<br>45-54          |
| <b>Asian Indians Subcontinent</b><br>India<br>Mauritius<br>Pakistan<br>Singapore<br>South Africa<br>UK | Ramachandran<br>Dowse<br>Shera<br>Tan<br>Omar<br>Simmons | 35-54<br>35-44<br>> 35<br>30-39<br>≥ 35<br>40-49 |
| <b>Pacific Islands</b><br>Nauru<br>Tonga   | Zimmet<br>Colagiuri                                      | > 25<br>> 30                                     |
| <b>Arabic Populations</b><br>Iran<br>Sultanate of Omar   | Amini<br>Asfour  | 60-69<br>40-49                                   |

### Summary – Age data

- AusDiab has provided up to date information on age-specific prevalence rates for undiagnosed Type 2 diabetes in Australia
- These data indicate that in the general Australian population a prevalence of:
  - 5% undiagnosed Type 2 occurs at age 55 and over
  - 2.5% undiagnosed Type 2 diabetes occurs at age 45 and over
- Aboriginal and Torres Strait Islanders have higher prevalences of undiagnosed Type 2 diabetes at younger ages than Caucasian populations and reach levels of 5% prevalence of undiagnosed diabetes by at least age 35
- Certain ethnic groups represented in Australia have a high prevalence of diabetes which is evident at a younger age
- Available data suggest that people from non-English speaking background the Pacific Islands, Indian subcontinent and of Chinese origin should be considered for testing for undiagnosed Type 2 diabetes from age 35 years and over

### 4. Obesity

Obesity in adult life is a well established risk factor for the future development of Type 2 diabetes. The focus of this review of the relationship between weight and Type 2 diabetes has been on quantitating the level of risk for undiagnosed Type 2 diabetes and for the future development of diabetes, and defining measures of weight which could be applied in routine clinical practice to identify individuals who should be tested for undiagnosed diabetes.

The WHO Report on Obesity (WHO, 1997) defines obesity as a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired. However, obese individuals differ not only according to their degree of excess fat but also in the regional distribution of that fat within the body and the latter affects the risks associated with obesity. Body mass index (BMI) provides the most useful population level measure of obesity but may not reflect the wide variation in body fat distribution. For the individual, measurement of waist circumference provides a simple and practical method of identifying

overweight individuals at increased risk of obesity-associated illness due to excess abdominal fat (WHO, 1997).

The WHO has adopted a classification of overweight in adults according to BMI and defines overweight as a BMI  $\geq 25$  and obesity as a BMI  $\geq 30$ . These BMI values are age and sex independent. The WHO also favours the use of waist circumference (WC) alone rather than waist:hip ratio (WHR) to assess abdominal fat, being a simpler measure and closely correlating with disease risk. WC measures of  $\geq 94$  cm for men and  $\geq 80$  cm in women define increased risk of obesity-associated disease and levels of  $\geq 102$  cm in men and  $\geq 88$  cm in women with substantially increased risk (WHO, 1997).

A number of studies have addressed the question of weight and the risk of having undiagnosed or developing Type 2 diabetes and these are summarised in Table 8. The majority of large studies have used self reported diabetes, and often self reported anthropometric measurements and weight changes. Despite these limitations, the study results have uniformly shown a relationship between weight and Type 2 diabetes. However, there have been some differences in the magnitude of the effect and in the relative importance of different measures of overweight.

An elevated BMI of approximately 30 or more increases the risk of Type 2 diabetes by 1.8 to 2.4-fold in absolute terms (Harris et al, 1987; Ruige et al, 1997; Baan et al 1999) or by 2.4 to 19-fold relative to a normal BMI (Colditz et al, 1990; Holbrook et al, 1990; Chan et al, 1994; Colditz et al, 1995; Carey et al, 1997; Ford et al, 1997; Resnick et al, 1998) in both men and women. Very few studies have reported results for newly diagnosed Type 2 diabetes and specific WHR measurements in populations relevant to Australia. The largest, the Nurses Health Study, demonstrated that the risk of Type 2 diabetes was increased 3.1-fold for high WHR and 5.1-fold with a large waist circumference (Carey et al, 1997). The findings in men were similar except that the increased risk with increasing WHR was accounted for only by men in the top 5% of WHR (Chan et al, 1994).

Weight gain, duration of overweight and rate of weight change are also risk factors for the development of Type 2 diabetes. Chan et al (1994) reported that the relative risk of diabetes of recent weight gain in men ( $> 13.6$  kg over the 5 year prior to entry into the study) was 4.5 (CI 2.4-8.2) compared with men whose weight changed by less than 4.5 kg and that weight gain from age 21 also increased the risk. Colditz et al (1995) reported similar results in women with weight gain of more than 5 kg from age 18 being associated with increased risk of diabetes independent of baseline BMI. In the NHANES study (Ford et al, 1997) weight gain of 11-19 kg increased risk by 2.7 (CI 1.8-3.9) compared with weight which remained within 5 kg of baseline. The effect of weight change may be different in different populations and may be influenced by gender. In Pima Indian men, the annual incidence of newly diagnosed diabetes was 5.7% in those gaining 3 kg or more each year compared with 1.7% in those losing weight. However in women weight gain only increased annual incidence of diabetes in those who were not initially overweight i.e. BMI  $< 27.3$  (Hanson et al, 1995).

Modan et al (1986) in a study from Israel, found that duration of BMI  $\geq 27$  was more closely associated with development of Type 2 diabetes than weight at time of diagnosis. The relationship with duration of obesity has also been reported for Pima Indians in whom annual incidence of new diabetes was 2.5% per year with duration of obesity (BMI  $\geq 30$ ) less than 5 years, 3.5% for duration of obesity between 5 and 10 years, and 6% with obesity for more than 10 years (Everhart et al, 1992). Similar findings were recently reported by Sakurai et al (1999) in Japanese men. Duration of obesity (BMI  $\geq 27.8$ ) for 0.1-9.9 years increased diabetes risk 7.6-fold (CI 3.1-18.9), obesity for 10-19.9 years 58.6-fold (CI 10.8-317) and obesity for 20 or more years 21.4-fold (CI 3.4-134).

**Table 8: Studies examining the relationship between weight and Type 2 diabetes**

| Study               | Population  | Age                              | DM criteria  | Relationship  | Comment  |
|---------------------|---|----------------------------------|--|---|--|
| Baan, 1999          | Rotterdam, Netherlands<br>1016 ND participants                                    | 55-75                            | OGTT   | BMI 1.8<br>(1.1-2.9)  | BMI $\geq 30$  |
| Carey, 1997         | Nurses Health Study, US<br>43 581 women<br>Follow up 1994                         | 30-55<br>at entry                | Self reported<br>diabetes and<br>weight              | BMI: 11.2 (7.9-15)<br>WHR:3.1 (2.3-4.1)                                       | BMI $\geq 29.9$ v $\leq 20.1$ ; WHR $\geq 0.86$<br>v $\leq 0.70$ ; Wccircumference<br>$\geq 92$ cm v $\leq 67$ cm: 5.1 (2.9-8.9) |
| Cassano, 1992       | VA Aging Study,<br>1972 males, follow up 18 y                                     | 22-80                            | OGTT (100g)  | BMI 1.8<br>(1.1-3.0)  | Annual incidence of NDM 0.6%<br>BMI $\geq 26.9$ v $\leq 24.6$  |
| Chan, 1994          | US health professionals<br>27 983 males<br>Follow up 1992                         | 40-75<br>at entry                | Self reported<br>diabetes and<br>weight              | BMI 6.7<br>(3.8-12.0)   | BMI $\geq 29$ v $< 23$ ; WHR only<br>predictive among top 5%<br>WC $> 102$ v $< 88$ cm: 3.5(1.2-7.0)                             |
| Chou, 1994          | Kinmen Islands, Taiwan<br>3236 participants                                       | $> 30$                           | FPG 5.6-7.8<br>Then OGTT                             | BMI 2.0 (1.3-2.9)<br>WHR 2.1 (1.4-3.1)  | BMI $\geq 27$ M; $\geq 25$ F<br>WHR $\geq 0.93$ M; $\geq 0.88$ F   |
| Colditz, 1990       | Nurses Health Study, US<br>114281 females,<br>Follow up – 8 y                     | 30-55<br>at entry                | Self reported<br>diabetes &<br>weight                | BMI 19<br>(13.6-26.4)   | BMI $\geq 29$ v $\leq 22$  |
| Colditz, 1995       | Nurses Health Study, US<br>114281 females<br>Follow up – 14 y                     | 30-55<br>at entry                | Self reported<br>diabetes and<br>weight              | BMI 15.8<br>(12.7-19.8)   | BMI $\geq 29$ v $\leq 22$<br>Extension of Colditz 1990 study   |
| Feskens, 1989       | Zutphen, Netherlands<br>841 males, follow up 25 y                                 | 70-89                            | Medically<br>confirmed DM                            | BMI 2.4<br>(1.3-4.4)  | Comparisons (25 <sup>th</sup> v 75 <sup>th</sup> centile)<br>BMI $\leq 22.2$ v $\geq 25.8$                                       |
| Ford, 1997          | NHANES, US<br>8545 participants<br>Follow up – upto 10 y                          | $> 25$                           | Self reported or<br>from records                     | BMI 4.9<br>(2.8-8.6)  | BMI $\geq 29$ v $\leq 22$ : Weight gain 11-<br>19kg v weight within 5 kg of<br>baseline – 2.7 (1.8-3.9)                          |
| Gurwitz, 1994       | East Boston, US<br>2737 people, follow up 6 y                                     | $> 65$                           | New diabetes<br>treatment                            | BMI 2.4<br>(1.3-4.4)  | BMI $< 22$ v $\geq 26$   |
| Harris, 1987        | NHANES II, US, 15357<br>interviewed, 3772 OGTT                                    | 20-74                            | OGTT   | 2.0 (in people aged 45-<br>74)  | Obese $\geq 120\%$ IBW   |
| Holbrook,<br>1990   | Rancho Bernardo study, US,<br>1716 ND adults<br>Follow up 11.9 y                  | $\geq 40$ at<br>initial<br>study | OGTT   | BMI:<br>M 2.4<br>F 3.1  | BMI $\geq 32$ v $\leq 23$  |
| Modan, 1986         | Israel GOH study<br>2140 ND participants<br>Follow up – mean 10 y                 | 28-57<br>at entry                | OGTT   | Past BMI $\geq 27$<br>2.4 (1.6-3.5)<br>Current BMI $\geq 27$ 1.2<br>(0.8-1.8) | BMI $\geq 27$ v $< 23$   |
| Njolstad, 1998      | Finnmark study, Norway<br>11654 ND people,<br>Follow up 12 y                      | 35-52                            | Questionnaire<br>& doctor/<br>record verified        | 5.5 (3.0-10) M<br>9.2 (4.3-20) F  | BMI $< 27$ v 29-31.9   |
| Perry, 1995         | British Heart Study<br>7735 men<br>Follow up 12.8 y                               | 40-59                            | RBG initial<br>Questionnaire at<br>follow up         | BMI 7.3<br>(3.4-15.6)   | BMI $> 27.9$ v $< 22.9$  |
| Resnick, 1998       | NHANES, US<br>9852 white participants<br>Follow up – 20 y                         | 25-74                            | Self reported or<br>obtained from<br>records         | BMI<br>4.3 M<br>2.2 F   | BMI $\geq 30$ v $< 26$   |
| Ruige, 1997         | Hoorn study, Netherlands<br>2364 ND participants                                  | 50-74                            | OGTT   | BMI 2.4<br>(1.4-4.2)  | BMI $> 30$ M; $> 29$ F   |
| Sakurai, 1999       | Sotestu study, Japan<br>1598 males<br>Weight measured in routine<br>health checks | $\geq 30$                        | OGTT or<br>diagnosed DM                              | Related to duration of<br>obesity   | OR new DM duration BMI $\geq 27.8$<br>0.1-9.9y 7.6 (3.1-18.9)<br>10-19.9y 58.6 (10.8-317)<br>$\geq 20$ y 21.4 (3.4-134)          |
| Shaper, 1997        | British Heart Study<br>7735 men (7575 ND men)<br>Follow up 14.8 y                 | 40-59                            | RBG ( $\geq 11.1$ )<br>Questionnaire at<br>follow up | BMI 9.7<br>(4.6-20.4)   | BMI $\geq 30$ v 20   |
| Shaten, 1993        | MRFIT Usual Care<br>6438 males, follow up 5 y                                     | 35-57                            | 1h OGTT, FPG<br>at follow up                         | BMI 2.2<br>(1.9-2.6)  | BMI 5 unit increments  |
| Vanderpump,<br>1996 | Whickhan survey, UK<br>1877 people<br>Follow up 20 y                              | $> 18$                           | History of<br>diabetes or<br>elevated FPG            | BMI<br>2.2M (1.5-3.3)<br>1.8 F (1.1-2.9)                                      | Assessed as age related 95 centile   |
| Welborn, 1997       | Australian Diabetes<br>Screening Study 1994/95<br>50859 people assessed           | $> 40$                           | Risk factor<br>questionnaire<br>RPG $> 5.5$ OGTT     | 2.2<br>(2.0-2.4)  | Self reported overweight   |

WC=waist circumference; ND = non-diabetic;

RPG=random plasma glucose; FPG=fasting plasma glucose; OGTT=75g glucose and WHO criteria unless indicated

## Summary – Obesity data

- Obesity is a major risk factor for the development of Type 2 diabetes
- Most of the available data has reported this risk in relation to BMI
- A BMI  $\geq 30$  results in a 2-fold increase in the risk of Type 2 diabetes
- This 2-fold increase in risk means that obesity can be combined as a risk factor with age of 45 and over to result in a 5% prevalence of undiagnosed diabetes
- Increased WHR and weight circumference are also associated with increased risk of Type 2 diabetes but available data do not allow quantitation of risk relative to a clinically applicable measurement level
- Weight gain and duration of obesity are also important factors in determining the occurrence of Type 2 diabetes

### 5. Family history

Family history of Type 2 diabetes is a recognised risk factor for the development of Type 2 diabetes in another family member. The lifetime risk of developing Type 2 diabetes is estimated at 40% if one parent has Type 2 diabetes (Kobberling, 1992). Comparing studies which have attempted to quantitate the actual risk conferred by a positive family history is limited by the usual study methodological problems which have already been noted. Reporting bias may also be introduced by the family member not knowing whether another family member had Type 2 diabetes. In addition, few studies have attempted to confirm or establish the diagnosis of diabetes in family members. A further problem is that not all studies have been consistent in the definition of family member, although most have considered either first degree relatives or parents with diabetes.

Table 9 summaries recent studies which have quantitated the effect of a positive family history on people with newly diagnosed Type 2 diabetes. All studies have consistently shown approximately a 2-fold increase in undiagnosed Type 2.

Most studies have reported that the effect is not gender specific, although there have been some exceptions with Mooy et al (1995) reporting a positive effect only in males and Sugimori (1998) only in females. There have also been conflicting reports as to whether diabetes in the mother or father is more closely associated with diabetes in a sibling. For example, Mitchell et al (1993) found that in both Mexican Americans and non-Hispanic whites, men with a parental history of diabetes had a higher prevalence of Type 2 diabetes, no matter which parent had diabetes, while in women only a maternal history was associated with a higher prevalence of diabetes. However, the same authors failed to confirm this in a subsequent study in Mexican Americans (Mitchell et al, 1995). The current data are therefore inconclusive on this point.

One report suggests that the effect of family history may also be modified by age. Costa et al (1998) studies 205 non-diabetic siblings of people with Type 2 diabetes. In comparison with the general population, at any age group, Type 2 diabetes was more common in people with a family history of Type 2 diabetes. For people aged 45 to 54 years the occurrence of undiagnosed diabetes was increased 2.8-fold compared with a 4.8-fold increase in people aged 55-64.

## Summary – Family history data

- Family history of Type 2 diabetes is a risk factor for undiagnosed Type 2 diabetes in other family members
- People with a positive family history of Type 2 diabetes have at least a 2-fold increased chance of having undiagnosed Type 2 diabetes

- This 2-fold increase in risk means that family history can be combined as a risk factor with age of 45 and over to result in a 5% prevalence of undiagnosed diabetes
- Most of the data about family history relates to first degree relatives – parents, siblings or both
- The evidence as to whether the increase in risk is gender specific is inconclusive

**Table 9: Studies examining the relationship between family history and Type 2 diabetes**

| Reference        | Population  | Age                     | DM criteria                               | Relationship#                      | Comment   |
|------------------|---|-------------------------|---|------------------------------------|---|
| Baan, 1999       | Rotterdam Diabetes Study, Netherlands<br>1016 ND participants   | 55-75                   | OGTT                                      | 1.9<br>(1.3-30.1)                  | FH= 1 <sup>st</sup> degree relative   |
| Boer, 1996       | Zutphen Elderly Study, Netherlands, 468 men   | 69-90                   | OGTT unless KDM                           | 3.9 (1.9-7.9)                      | FH = 1 <sup>st</sup> degree relative<br>NGT: 6.8%<br>ND: 20.5%  |
| Chan, 1994       | US male health professionals, 27 983 males  | 40-75 at entry to study | Self reported diabetes                    | 2.3 (1.8-3.0)                      | FH = 1 <sup>st</sup> degree relative  |
| Costa, 1998      | Catalonia Spain<br>205 ND children, siblings of Type 2 DM   | < 75                    | OGTT                                      | Age:<br>45-54 – 4.8<br>55-64 – 2.8 | FH = sibling or child of person with Type 2 DM  |
| Grill, 1999      | Stockholm Diabetes Prevention Programme, Sweden, 3128 males (1622 FH+, 1506 FH-)                      | 35-56                   | OGTT                                      | One relative:<br>4.1<br>(2.1–8.3)  | >One 1 <sup>st</sup> degree relative<br>5.0 (1.8-14.1)<br>Two 2 <sup>nd</sup> degree relatives<br>2.1 (0.6-7.6) |
| Groop, 1996      | Botnia Study, Finland<br>2152 1 <sup>st</sup> degree relatives of people with KDM and 528 FH- spouses | 51 Mean                 | OGTT                                      | ND:<br>2.9% FH -<br>7.3% FH +      | FH = 1 <sup>st</sup> degree relative  |
| Harris, 1987     | NHANES II<br>15357 interviewed<br>3772 had OGTT   | 20-74                   | OGTT                                      | 1.9 in people aged 45-74           | FH= either parent with DM   |
| Kawakami, 1997   | Japan<br>2312 males   | 18-53                   | Glycosuria, FPG & OGTT if FPG ≥ 6.1       | 2.4 (1.2-4.7)                      | FH = 1 <sup>st</sup> degree relative  |
| Kekalainen, 1999 | Kuopio, Finland<br>393 siblings at baseline, 309 at follow up   | 45-64                   | OGTT                                      | 3.3<br>(1.5-6.9)                   | FH=sibling  |
| Mooy, 1995       | Hoorn study, Netherlands<br>2484 people   | 50-75                   | OGTT                                      | NGT ND<br>M 23% 43% F<br>27% 35%   | FH = grandparents, siblings, children<br>Sig for men, NS for women  |
| Mykkanen, 1990   | Kuopio, Finland,<br>1300 participants   | 65-74                   | OGTT                                      | No DM 27%<br>ND 39%                | FH=parent or sibling with Type 2 diabetes   |
| Ohlson, 1988     | Gothenberg, Sweden<br>766 males   | 54 mean                 | Self reported, FPG in 1980<br>OGTT (100g) | 2.4                                | FH = first and second degree relatives  |
| Ruige, 1997      | Hoorn study, Netherlands<br>2364 participants   | 50-74                   | OGTT                                      | 1.9<br>(1.3-2.9)                   | FH= parent or sibling with DM   |
| Shaten, 1993     | MRFIT study<br>6438 males<br>Usual Care part of study   | 35-57                   | OGTT (1h PG only)                         | 2.0<br>(1.5-2.6)                   | FH=either parent with DM  |
| Sugimori, 1998   | MHTS, Tokyo, Japan<br>2573 participants   | 18-69                   | FBG > 6.1 or therapy                      | 1.7 F<br>(1.2-2.4)                 | Family member not specified   |
| Todoraki, 1994   | Fukuoka, Japan<br>2407 males  | 48-56                   | OGTT                                      | 2.7<br>(1.1-6.6)                   | FH=parent with DM   |
| Welborn, 1997    | Australian Diabetes Screening Study<br>50859 people assessed  | > 40                    | Questionnaire<br>RPG > 5.5<br>OGTT        | 2.1 (1.9-2.5)                      | FH=relative with DM   |

FH=family history; ND = newly diagnosed; KDM=known diabetes; RPG=random plasma glucose; FPG=fasting plasma glucose; RBG=random blood glucose; OGTT=75g glucose and WHO criteria unless indicated  
# - Odds ratio or relative risk unless otherwise stated

## 6. Hypertension

Hypertension and Type 2 diabetes are known to coexist. People with Type 2 diabetes have an increased prevalence of hypertension. In the Hypertension in Diabetes Study, 39% of newly presenting people with Type 2 diabetes had hypertension (Hypertension in Diabetes Study Group, 1993). This section of the review considers the association of hypertension and undiagnosed Type 2 diabetes or the future development of Type 2 diabetes.

Methodological differences which influence the direct comparison of studies which have addressed this question include differences in the definition of hypertension, either above a certain level or on antihypertensive medication or both; choice of blood pressure levels higher than those commonly used to define hypertension today; methods used to define diabetes; differences in populations studied and selection bias of people with hypertension.

Despite these differences most studies (Table 10) have shown that hypertension is associated with a 1.6 to 2.6-fold increase in the chance of an individual having undiagnosed Type 2 diabetes (Saad et al, 1990; Chou et al, 1994; Ruige et al, 1997; Welborn et al, 1997; Baan et al, 1999). Bog-Hansen et al (1998) performed a community based study in which they investigated people with hypertension for undiagnosed Type 2 diabetes and found a high rate of previously undiagnosed Type 2 diabetes of 26%: 17% in people under age 70 and 31% in people aged 70 or over. However, this study did not include a control group of age matched people without hypertension.

Similarly, studies which have prospectively examined the risk of having hypertension on the future development of Type 2 diabetes have reported a 1.4-2.5-fold increased risk (Helmrich et al, 1991; Gurwitz et al, 1992; Mykkanen et al, 1994; Feskens et al, 1995; Sugamori et al, 1998; Hayashi et al, 1999) while Vanderpump et al (1996) reported a 3.5-fold increase in annual incidence of Type 2 diabetes in men and a 4-fold increase in women.

One of the issues in exploring the reason behind this association has been the question as to whether this increase in risk is secondary to the antihypertensive treatment or due to the underlying metabolic abnormalities of hypertension. Most of the studies which have addressed this question have focussed on risk associated with use of beta blockers or thiazide diuretics, agents which are not commonly used in Australia for the management of hypertensive people with Type 2 diabetes. In a study which included a wide range of antihypertensive therapies, no association was found between a particular antihypertensive therapy but the occurrence of diabetes requiring therapy was related to the intensity of therapy, assessed as the number of agents used (Gurwitz et al, 1992). In a recently published study, Hayashi et al (1999) reported that the annual incidence of Type 2 diabetes was similar for hypertensive men who were, or were not, on treatment (RR 1.8 v 1.6).

The study of Hayashi et al (1999) also provides results in relation to blood pressure readings more in keeping with current levels for defining hypertension and noted that the risk of new Type 2 diabetes was increased 1.8-fold in men with blood pressure readings of 140/90 or above.

### Summary – Hypertension data

- Hypertension is associated with approximately a 2-fold increase in an individual having undiagnosed Type 2 diabetes or developing Type 2 diabetes in the future
- This 2-fold increase in risk means that hypertension can be combined as a risk factor with age of 45 and over to result in a 5% prevalence of undiagnosed diabetes

- while the reason for the increase in risk associated with hypertension has yet to be elucidated, there is little evidence to suggest that this increase in risk is associated with modern antihypertensive therapies

**Table 10: Studies examining the relationship between hypertension and Type 2 diabetes**

| Reference        | Population  | Age            | DM criteria                                | Relationship #   | Comment   |
|------------------|---|----------------|--|--|---|
| Baan, 1999       | Rotterdam, Netherlands<br>1016 participants   | 55-75          | OGTT                                       | 1.6<br>(1.04-2.4)  | HT=use of medication  |
| Bog-Hansen, 1998 | Skara Hypertension and Diabetes Project, Sweden   | Mean 69        | FBG $\geq 6.7$ x2<br>OGTT if FBG x2 5.5-6. | 26% of people with HT had ND<br>Age <70 17% ND<br>Age $\geq 70$ 31% ND                               | HT dBP $\geq 90$ or treatment   |
| Chou, 1994       | Kinmen Islands, Taiwan<br>3236 participants   | > 30           | FPG 5.6-7.8<br>Then OGTT                   | 1.7<br>(1.1-2.6)   | HT BP > 160/95  |
| Feskens, 1995    | Zutphen study Finland<br>470 males after 30y  | 70-89          | OGTT                                       | 2.2<br>(1.4-3.4)   | HT=BP $\geq$ 160/90 or on treatment   |
| Gurwitz, 1992    | New Jersey, US<br>11855 subjects starting OHA or insulin if taking antiHT treatment<br>11855 controls | $\geq 35$      | Starting OHA or insulin                    | OR of people with treated HT starting diabetes treatment 1.6-1.8 – no matter which single medication | HT= use of medication   |
| Hayashi, 1999    | Osaka Health Study, Japan<br>7594 males   | 35-61          | FPG ADA<br>Or OGTT                         | 1.8<br>(1.4-2.2)   | HT=BP $\geq$ 140/90 or medications<br>RR - excluding people on medication 1.6 (1.3-2.1) |
| Helmrich, 1991   | University of Pennsylvania alumni<br>5990 men in 1962   | 39-62 at entry | Questionnaire – DM diagnosed by physician  | 1.8<br>(1.2-2.7)   | HT=history of HT  |
| Mykkanen, 1994   | Kuopio, Finland<br>805 people, follow up 3.5y   | 65-74          | OGTT                                       | 2.5<br>(1.4-4.7)   | HT=BP $\geq$ 160/95 or on Medication  |
| Ruige, 1997      | Hoorn study, Netherlands<br>2364 participants   | 50-74          | OGTT                                       | 2.3<br>(1.5-3.5)   | HT = use of medication  |
| Saad, 1990       | Pima Indians, Arizona US<br>2873 people   | 18-92          | OGTT                                       | 2.6<br>(2.0-3.2)   | HT=BP $\geq 160/95$ or treatment<br>HT- No DM, 4.9%, NDM 17.9%, KDM 30.4%               |
| Sugimori, 1998   | MHTS, Tokyo, Japan<br>2573 participants<br>Follow up – 16 y   | 18-69          | FBG > 6.1<br>Or diabetes therapy           | 1.6<br>(1.3-2.0)   | HT=BP $\geq 160/95$ or treatment  |
| Vanderpump, 1996 | Whickhan survey, UK<br>1877 survivors<br>Follow up 20 y   | > 18           | History of diabetes or elevated FPG        | 3.5 M<br>4.0 F   | Annual incidence of NDM was 0.2%  |
| Welborn, 1997    | Australian Diabetes Screening Study 1994/95<br>50859 people assessed                                  | > 40           | Risk factor questionnaire<br>RPG>5.5OGTT   | 2.2<br>(1.9-2.4)   | Self reported HT  |

HT=hypertension; dBP=diastolic blood pressure; ND=newly diagnosed; KDM=known diabetes; RPG=random plasma glucose; FPG=fasting plasma glucose; RBG=random blood glucose; OGTT=75g glucose and WHO criteria unless indicated; ADA= American Diabetes Association

# - Odds ratio or relative risk (RR) unless otherwise stated

## 7. Cardiovascular disease

People with diabetes have at least a 2-fold higher risk of developing cardiovascular disease than nondiabetic individuals (Gerstein, 1998). The question addressed here is whether there is an increased prevalence of undiagnosed Type 2 diabetes in people with cardiovascular disease. For the purpose of this review cardiovascular disease includes both coronary artery disease and ischaemic cerebrovascular disease.

Only a few studies have addressed this question by testing people with cardiovascular disease with an OGTT. Farrer et al (1995) tested 353 consecutive non-diabetic people undergoing coronary artery bypass surgery for undiagnosed diabetes 3 and 12 months after surgery. The prevalence of undiagnosed Type 2 diabetes was 4.4% at 3 months and 4.6% at 12 months. Katz et al (1994) tested 73 non-diabetic people aged under 55 years who were undergoing investigation for possible coronary artery disease. Overall 6.8% had undiagnosed Type 2 diabetes. However, in the 42 with angiography confirmed coronary artery disease, 12% had undiagnosed Type 2 diabetes, a rate much higher than that found in the NHANES II study (Harris et al, 1987) for people under age 55 years. Madsen et al (1986) studied 214

consecutive people admitted to coronary care units with acute myocardial infarction. Nineteen people without a prior history of diabetes had blood glucose levels of 9 mmol/l or higher and the 15 who survived for 2 months had an OGTT. Diabetes was confirmed in 9, giving an overall prevalence of undiagnosed Type 2 diabetes of 4.5%. However the true prevalence may have been higher because people with lower random blood glucose levels were not tested and could have had undiagnosed diabetes. Oswald et al (1984) examined people without diabetes admitted to the Whittington Hospital after an acute myocardial infarction. Of the 109 survivors, 69 had an oral glucose tolerance test within 7 to 10 days of admission of whom 15.9% had levels consistent with undiagnosed diabetes. Forty one of these had a repeat OGTT after 3 months revealing a prevalence of Type 2 diabetes of 7.3%, with many of the originally abnormal tests reverting to normal. Those who were positive at both times of testing had elevated glycated haemoglobin levels at the time of admission.

These studies confirm that people with coronary artery disease have an increased risk of having undiagnosed Type 2 diabetes.

Few data are available to examine the relationship between stroke and undiagnosed diabetes and no study was identified which examined this question using an OGTT. Gray et al (1987) studied 86 people admitted to hospital having had a stroke. Twenty eight percent of people without a prior diagnosis of Type 2 diabetes had an elevated admission glycated haemoglobin and may have had undiagnosed diabetes. Two other studies have reported 6% and 42% respectively of people with stroke or transient ischaemic episodes had elevated admission glycated haemoglobin levels (Riddle & Hart, 1982; Oppenheimer et al, 1985). Despite these wide variations, these studies all showed the same trend and are suggestive of a significant percentage of undiagnosed Type 2 diabetes in people with stroke.

The study by Oswald et al (1984) raises the issue of when people with cardiovascular disease should be tested for undiagnosed diabetes, since testing in the days immediately following the myocardial infarction yielded approximately twice the rate of undiagnosed diabetes compared with testing at 3 months, although the groups of patients tested were not all the same individuals.

Stress hyperglycaemia is a well documented phenomenon (Mizock, 1995). In the clinical context of an acute event, such as a myocardial infarction, it may be difficult to distinguish between previously undiagnosed diabetes or hyperglycaemia as a metabolic response to stress. There are data indicating that treatment of hyperglycaemia during admission associated with an acute myocardial infarction improves prognosis (Malmberg et al, 1997). On the other hand an incorrect diagnosis of diabetes may be made if an individual is tested in the period immediately after the event (Oswald et al, 1984). A practical approach to this problem would be to correct the hyperglycaemia associated with an acute event but delay the definitive testing for 3 months. Measurement of glycated haemoglobin during the acute event may be helpful in clarifying the diagnosis if the level is elevated (Oswald et al, 1984), although only limited data are available on this point.

### **Summary – Cardiovascular disease data**

- Cardiovascular disease (including cerebrovascular disease) occurs commonly in people with diabetes
- The prevalence of undiagnosed Type 2 diabetes in people with coronary artery disease ranges from 4.4% to 12%
- People with cardiovascular disease should be routinely tested for undiagnosed Type 2 diabetes

- A definitive diagnosis of undiagnosed Type 2 diabetes should not be made during an acute cardiovascular event and results suggestive of undiagnosed diabetes should be confirmed 3 months after the acute event

### 8. *Polycystic ovary syndrome*

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age and recent prevalence studies suggest that 5-10% of premenopausal women have the full syndrome (Dunaif, 1995). PCOS is characterised by hyperandrogenism and chronic anovulation after the exclusion of secondary causes. The presence of polycystic ovaries diagnosed by ultrasonography is consistent with, but not essential for the diagnosis (Dunaif, 1995). Polycystic ovaries without the endocrine abnormalities appear to be of no clinical significance since only women with hyperandrogenism and chronic anovulation are insulin resistant.

Women with PCOS have a degree of insulin resistance similar to that of people with Type 2 diabetes which is additive to that of obesity (Davidson, 1995). Fifty percent of women with PCOS have a unique disorder of insulin action due to decreased insulin induced receptor autophosphorylation (Dunaif, 1995).

All studies which have examined the prevalence of undiagnosed Type 2 diabetes in women with PCOS have found an increased prevalence. Legro et al (1999) have prospectively studied 254 non-diabetic women (age 14-44 years) with PCOS and compared the findings with 80 women (age 18-40 years) without PCOS. Of the PCOS women, 7.5% had newly diagnosed Type 2 diabetes and 31.1% had IGT while in the control group none had diabetes and 14% had IGT. The control group findings are comparable to those of the NHANES II study (Harris et al, 1987) in which the prevalence of new diabetes was 1% and IGT 7.8%.

Similar prevalence rates have been reported by Ehrmann et al (1996) in 68 consecutive women with PCOS (mean age 28.1 years; mean BMI 40.6) who were investigated with an OGTT. The prevalence of undiagnosed diabetes was 5.9%. The annual incidence of subsequent development of diabetes over a 3.4 year follow up in women with initial normal glucose tolerance was 0.11 cases per person year. Dahlgren et al (1992) studied 33 women aged 40-59 with PCOS who had had a wedge resection 22-31 years earlier. Fifteen percent had developed diabetes requiring treatment with diet or medication compared with 2.3% in age matched controls. An increased risk of diabetes has also been reported in the preliminary findings of a case controlled cohort study in the UK (Wild et al, 1998). Cohort members with PCOS had a 2.2 (CI 1.02-4.7) increased risk of diagnosed diabetes compared with the control group.

The prevalence of undiagnosed Type 2 diabetes in women with PCOS is related to weight. Legro et al (1999) found that 78% of women in the were overweight (BMI  $\geq$  27). PCOS women with BMI  $\geq$  27 has a prevalence of undiagnosed diabetes of 6.0% whereas in PCOS women with BMI  $<$  27 the prevalence was 1.5%.

Ethnic background does not seem to influence the prevalence of undiagnosed diabetes in women with PCOS, even though one study reported ethnic differences in insulin and glucose responses between white and Indian women with PCOS (Norman et al, 1995). Legro et al (1999) found similar rates in an urban ethnically diverse population and a predominantly non-Hispanic white population.

## **Summary – Polycystic ovary syndrome data**

- Women with PCOS have an increased prevalence of undiagnosed Type 2 diabetes of at least 5%
- This increase in prevalence of undiagnosed Type 2 diabetes applies particularly to women with PCOS who are obese
- PCOS, especially in obese women, is a risk factor for undiagnosed Type 2 diabetes and these women should be regularly tested for undiagnosed diabetes

### **9. Other risk factors considered**

#### **a] Smoking**

Smoking is a well documented risk factor for ill health and is a major contributor to the development of diabetes related microvascular and macrovascular complications (NHMRC, 1997; Haire-Joshu et al, 1999). Therefore, people with diagnosed diabetes should avoid smoking. The specific question addressed here relates to the evidence about smoking as an independent risk factor for the presence of undiagnosed diabetes or for the future development of Type 2 diabetes. Smoking has been shown to increase insulin resistance and to diminish insulin secretion (Fрати et al, 1996) both of which are associated with the development of Type 2 diabetes.

Table 11 summarises the review of the literature which addresses this topic. These studies have addressed various aspects of a possible relationship between diabetes and smoking including current and former smoking and the quantity of cigarettes smoked. Several studies have failed to show any relationship between current smoking and the presence of undiagnosed Type 2 diabetes or its future development (Ohlson et al, 1988; Fujimoto et al, 1990; Cassano et al, 1992; Shaten et al, 1993; Mooy et al, 1995; Rodriguez et al, 1996; Njolstad et al, 1998). A recent 30 year retrospective analysis showed a negative association between current smoking and impaired glucose tolerance (diabetes and IGT combined) but smoking was associated with an increased risk of premature death in participants not surviving until the 30 year follow up (Qiao et al, 1999).

Studies which have reported an association have differed in their findings. In men an increased risk with some aspects of smoking was found in 4 Japanese studies (Todoraki et al, 1994; Kawakami et al, 1997; Sugimori et al, 1998; Uchimoto et al, 1999), in the US male health professionals study (Rimm et al, 1995) and in the British Regional Heart Study (Perry et al, 1995). However the findings have been inconsistent. Rimm et al (1995) found an increased risk in former smokers and in current smokers who smoked more than 15 cigarettes a day. Perry et al (1995) found no increase in former smokers but an increase in current smokers which was not related to number of cigarettes smoked while Todoraki et al (1994) found an increase in former and current smokers at all levels of tobacco consumption and Uchimoto et al (1999) reported no increase in former smokers and an increase in all levels of consumption for current smokers. Rimm et al (1993) also reported an increased risk in women from the Nurses Health Study for former smokers and current smokers consuming more than 15 cigarettes daily but Sugimori et al (1998) did not find an increased risk in women in their study.

**Table 11: Studies examining the relationship between smoking and Type 2 diabetes**

| Reference       | Population  | Age                               | DM criteria  | Relationship#                                   | Comment   |
|-----------------|---|-----------------------------------|--|---|---|
| Cassano, 1992   | VA Aging Study, 1972 males follow up 18 y                                   | 22-80                             | OGTT (100g)  | Current: 1.1 (0.7-1.8)<br>Former: 1.5 (1.0-2.4) | Annual incidence of NDM 0.6%<br>Current smoker amount not Defined   |
| Feskens, 1989   | Zutphen study, Netherlands 841 males studied again after 25 years           | 40-59 at entry<br>70-89 at review | Self reported medically confirmed DM                     | 2.7 (1.1-6.6)                                   | Smoking 0 v $\geq 20$   |
| Fujimoto, 1990  | Japanese-American Community Heart Study 219 men                             | Mean 60                           | OGTT   | NS  | No difference between never smoked, present or current smoker and glucose tolerance   |
| Kawakami, 1997  | Japan 2312 males Follow up 8 y  | 18-53                             | Glycosuria<br>If positive FPG and OGTT if FPG $\geq 6.1$ | 1.1 (0.3-4.3)<br>3.3 (1.2-9.1)<br>3.2 (1.1-9.8) | Never smoked v<br>1-15 cigs/day<br>16-25 cigs/day<br>>25 cigs/day   |
| Mooy, 1995      | Hoorn study, Netherlands 2484 people  | 50-74                             | OGTT   | NS  | No differences between current smokers yes v no and NDM   |
| Njolstad, 1998  | Finmark study, Norway 11654 ND people Follow up 12 y                        | 35-52                             | Questionnaire & record verified                          | 0.8 (0.6-1.3) M<br>0.8 (0.5-1.3) F              | Daily smoking – yes v no  |
| Ohlson, 1988    | Gothenberg, Sweden 766 ND males Follow up 13.5 y                            | 54                                | Self reported, FPG, in 1980 100g OGTT                    | NS  |   |
| Perry, 1995     | British Regional Heart Study 7735 men Follow up 12.8 y                      | 40-59                             | RBG initial Questionnaire only at follow up              | See comments                                    | Never smoked<br>V current smokers 1.5 (1.0-2.2)<br>V ex smokers 1.2 (0.8-1.8)<br>No association – number smoked   |
| Qiao, 1999      | Finland, 663 survivors in 1989, follow up 30 years                          | 49-59 at entry                    | OGTT 1984 & 9, Unless KDM                                | See comments                                    | Current smoking V abnormal GT 0.4 (0.2-0.7)   |
| Rimm, 1993      | Nurses Health Study, US 114247 females Follow up – 12 y                     | 30-55 at entry in 1976            | Self reported diabetes                                   | See comments                                    | Nonsmokers<br>v exsmokers 1.2 (1.02-1.4)<br>v 1-14cig/day 0.9 (0.7-1.2)<br>v 15-24cigs/day 1.2 (1.01-1.5)<br>v $\geq 25$ cigs/day 1.5 (1.2-1.9)                       |
| Rimm, 1995      | US male health professionals 41860 at entry Follow up 1992 6 year follow up | 40-75 in 1986                     | Self reported diabetes                                   | See comments                                    | Nonsmokers<br>v exsmokers 1.3 (1.0-1.7)<br>v 1-14cig/day 1.0 (0.4-3.0)<br>v 15-24cigs/day 2.7 (1.6-4.6)<br>v $\geq 25$ cigs/day 2.1 (1.2-3.7)                         |
| Rodriguez, 1996 | Honolulu Heart Study, US Japanese American men 1900                         | 71-93                             | OGTT   | NS  | Prevalence of current smoking between people with NDM and No DM   |
| Shaten, 1993    | MRFIT study 6438 Follow up 5 y  | 35-57                             | OGTT (1h PG only), FPG at follow up                      | NS  | Smoking No DM 63% v NDM 53%   |
| Sugimori, 1998  | MHTS, Tokyo, Japan 2573 participants Follow up – 16 y                       | 18-69                             | FBG > 6.1 or diabetes therapy                            | 1.4 M (1.03-1.8)<br>NS F                        | Smoking v never or past smoker  |
| Todoroki, 1994  | Fukuoka, Japan 1986-90 2407 males   | 48-56                             | OGTT   | Significant see comments                        | Never smoked<br>v past 2.6 (1.2-5.8)<br>v <15cigs/day 4.1 (1.2-13.3)<br>v 15-24cigs/day 3.5(1.6-7.7)<br>v $\geq 25$ cigs/day 4.2 (1.8-9.6)                            |
| Uchimoto, 1999  | Osaka Health study, Japan 6250 men Follow up 4-16 y                         | 35-60                             | FPG $\geq 7$ or physician diagnosis                      | Significant see comments                        | Non-smokers<br>v past smokers 1.1(0.8-1.5)<br>v current 1.5 (1.1-1.9)<br>v 1-20 cigs/day 1.4(1.1-1.9)<br>v 21-30cigs/day 1.4(1.02-1.9)<br>v >30 cigs/day 1.7(1.2-2.5) |

ND=newly diagnosed; KDM=known diabetes; RPG=random plasma glucose; FPG=fasting plasma glucose; RBG=random blood glucose; OGTT=75g glucose and WHO criteria unless indicated;  
# - Odds ratio or relative risk (RR) unless otherwise stated

### Summary – Smoking data

- The evidence supporting a role for smoking in identifying people with undiagnosed Type 2 diabetes or in predicting the future development of diabetes is equivocal
- There is insufficient evidence at the present time to recommend smoking for inclusion as a risk factor for identifying people with undiagnosed Type 2 diabetes

- This conclusion should be clearly separated from the overwhelming evidence (not reviewed here) of the health hazards associated with smoking both for people with and without diabetes

***b] Women with a history of giving birth to a large baby***

A prior history of giving birth to a large baby has been traditionally considered a risk factor for identifying women who may have undiagnosed Type 2 diabetes. The American Diabetes Association includes women delivering babies in excess of 4.1 kg (9lbs) in the high risk groups which should be actively screened for undiagnosed diabetes (ADA, 2000).

Definitional problems have been a major issue in studies in this field, especially in the selection of an appropriate reference range of normality (Schwartz & Teramo, 1999). Sacks (1993) performed a systematic review of foetal macrosomia and concluded that there is no universally accepted definition of foetal macrosomia. Many factors affect birth weight including maternal glucose tolerance, age, parity, ethnic background, weight, weight gain, smoking status and foetal gender which confound making evidence based conclusions about macrosomia (Sacks, 1993). Unfortunately, his review did not address the question of foetal macrosomia as an independent risk factor for the future development of Type 2 diabetes in the mother.

The majority of studies which suggest an association between birth weight and subsequent development of Type 2 diabetes were reported prior to 1960 (Larsson et al, 1986). In these studies old criteria were used to diagnose diabetes, a control group was rarely used and other risk factors for diabetes or macrosomia were not considered.

While different approaches have been used in the few recent studies which have attempted to address this question, only one prospective study has attempted to control for possible confounding factors in the mother which could contribute to having a macrosomic baby or for the future development of diabetes (eg previous glucose intolerance during pregnancy, obesity, maternal age, family history of diabetes etc) (O'Sullivan & Mahan, 1980).

In the Boston Gestational Diabetes Study, O'Sullivan & Mahan, (1980) followed 308 women with GDM and 328 women with normal glucose tolerance for up to 16 years. Birth of a large baby ( $\geq 4.1$  kg) was not associated with the development of Type 2 diabetes in either group. The relative risk, after adjustment for a wide range of potential confounding variables, was 0.9. However, a large baby in women with glucose intolerance during pregnancy was an independent risk factor for decompensation to diabetes.

Larsson et al (1986) prospectively studied 270 women who had an OGTT within the first week after delivery of which 179 were retested with an OGTT after 3-10 years and 236 were retested 22-27 years after the index pregnancy. 6.8% of women giving birth to a baby weighing more than 4.5 kg had developed Type 2 diabetes, a rate 6 times greater than in control women giving birth to babies weighing less than 4.5 kg. However, the women with large babies also had a high prevalence of recognised risk factors for diabetes eg obesity and a family history of diabetes. The authors concluded that giving birth to a single large baby is of minor, if any, importance to the subsequent development of Type 2 diabetes.

Cowie and Harris (1995) reported data from the 1989 National Health Interview Survey and NHANES II. Women with previously undiagnosed diabetes reported a mean 0.5 babies weighing  $\geq 4.1$  kg (0.4 in women aged 20-49 and 0.6 in women aged 50-74) compared with a mean of 0.3 babies weighing  $\geq 4.1$  kg in non-diabetic women (0.2 in women aged 20-49 and

0.5 in women aged 50-74). No information was provided as to whether these differences were significant.

McGuire et al (1996) performed a population-based case-control study using birth certificate data to assess risk of development of subsequent self reported diabetes in women having given birth to a macrosomic infant (> 4.0 kg) during the previous pregnancy. Non-diabetic women who had a macrosomic infant in their prior pregnancy were twice as likely to have developed diabetes by their subsequent pregnancy [CI 1.9 (1.1-3.4)]. However, this finding should be interpreted with caution because, as acknowledged by the authors, it is possible that women with macrosomic infants included women with undiagnosed gestational diabetes, a known risk factor for macrosomia.

Two studies have examined this question in relation to multiple risk factor assessment questionnaires. Ruige et al (1997) did not find a history of having given birth to a large baby useful, whereas Herman et al (1995) found that it was only helpful in women aged 65 or older in predicting the presence of undiagnosed diabetes.

### **Summary – Women with a history of giving birth to a large baby data**

- There is a lack of suitably designed studies which have addressed whether giving birth to a large baby increases the risk of the subsequent development of Type 2 diabetes in the mother
- Available data suggest little increased risk of future diabetes following previous birth of a large baby
- Use of previous birth of a large baby to identify women at increased risk of having undiagnosed Type 2 diabetes is not recommended

### ***c] Lipids***

The issue addressed here is whether blood lipid levels can be used to assess an individual for the presence of undiagnosed Type 2 diabetes or to predict the future development of Type 2 diabetes (Table 12). People with Type 2 diabetes commonly have elevated lipid levels at the time of diagnosis which often improve with improving glycaemic control. Studies which have reported the association of elevated lipids and newly diagnosed Type 2 diabetes have invariably reported the results as significant differences in mean values. The literature review failed to identify studies which distinguished between diagnosed and newly diagnosed Type 2 diabetes and which quantified risk according to actual lipid levels. In studies which included multivariate analyses of risk factors for Type 2 diabetes, lipid levels were considered as continuous variables. For example, Chou et al (1994) reported significantly increased odds ratios for newly diagnosed Type 2 diabetes for cholesterol values above 6.2 mmol/l and age-adjusted triglyceride values ranging from above 1.7 mmol/l in people aged 30 to 39 years to above 2.2 mmol/l in people age 50 years in univariate analyses. However in the multivariate analyses, cholesterol, triglycerides and HDL cholesterol were analysed as continuous variables.

In addition, studies invariably considered lipid levels without taking into account the use of lipid lowering therapy. Baan et al (1999) assessed the use of lipid lowering therapy (but not lipid levels) and reported a negative finding as a predictor of undiagnosed Type 2 diabetes.

A number of studies have addressed the question of lipid levels as a predictor for the future development of Type 2 diabetes and have shown an association with baseline triglyceride levels (Mykkanen et al, 1993; Chou et al, 1994; Austin et al, 1995; Perry et al, 1995). Only the study of Mykkanen et al (1993) specified a triglyceride level of 2.5 mmol/l above which this risk increased. However, other studies have not confirmed this finding (Ohlson et al,

1988; Charles et al, 1991; Shaten et al, 1993; Njolstad et al, 1998) while others have found an association in women but not men (McPhillips et al, 1990; Vanderpump et al, 1996). Triglyceride levels are related to body weight and adjustment for measures of weight eg BMI frequently change a significant univariate association into a non-significant result in a multivariate analysis. People with familial hypertriglyceridaemia may be an exception. Sane and Taskinen (1993) reported a 10 year prospective study of 56 people with familial hypertriglyceridaemia and demonstrated that the increased risk of developing Type 2 diabetes was increased in this cohort with a mean triglyceride level of 4.3 mmol/l.

Most studies have not shown an association between total cholesterol level and the future development of Type 2 diabetes (Ohlson et al, 1988; Feskens et al, 1989; McPhillips et al, 1990; Shaten et al, 1993; Austin et al, 1995; Perry et al, 1995; Vanderpump et al, 1996; Njolstad et al, 1998) although the study of Chou et al (1994) was an exception.

The results of studies which have reported the effect of HDL cholesterol levels have varied. Chou et al (1994) and Mykkanen et al (1993) showed an increased risk with low levels of HDL cholesterol while Njolstad et al (1998) reported an association only in women. However, other studies have found no association in either men or women (Shaten et al, 1993; Austin et al, 1995; Perry et al, 1995).

### **Summary – Lipid data**

- Studies fail to provide data as to whether specific lipid levels are associated with an increased risk of an individual having undiagnosed Type 2 diabetes
- The results of prospective studies do not provide a consistent finding as to whether abnormal lipid levels are associated with an increased risk of the future development of Type 2 diabetes
- Use of abnormal lipid levels is not recommended as a means of identifying people who may have undiagnosed Type 2 diabetes

### ***d) Physical inactivity***

Physical inactivity is an important risk factor for the future development of Type 2 diabetes. This topic has been extensively reviewed in the guideline on the Primary Prevention of Type 2 diabetes (Part 2 of this document).

Despite this evidence, physical inactivity has not been included as a factor to identify at risk individuals who should be tested for undiagnosed Type 2 diabetes because of the inability to accurately assess and quantitate physical activity in routine clinical practice.

Two recent population studies have addressed the predictive value of physical activity assessed by different methods. Baan et al (1999) found the inclusion of an assessment of physical activity useful in their predictive model of risk factors for Type 2 diabetes. In this study from the Netherlands, cycling was the variable which contributed most to discriminating between active and inactive people in predicting diabetes. The authors found use of the term ‘physical activity’ too broad and vague to derive a useful measure of activity. In Australia there is no simple equivalent activity to cycling which was used in the Netherlands study. Herman et al (1995) included assessment of ‘sedentary lifestyle’ (defined as little or no exercise during recreation and quite inactive during a usual day) and found that this was only predictive of the development of diabetes in specific subgroups of their population - obese people younger than 45 years of age, and in non-obese people aged 45 to 64.

Either of these definitions would be difficult to apply in a uniform way in routine clinical practice in Australia. If a simple and clinically useful index to quantitate physical activity becomes available and is shown to correlate with risk of undiagnosed Type 2 diabetes, then the decision taken here not to include physical activity as a risk factor in the routine assessment of an individual for the presence of undiagnosed Type 2 diabetes, should be reconsidered.

**Table 12: Studies examining the relationship between lipids and Type 2 diabetes**

| Reference        | Population  | Age   | DM criteria   | Relationship #   | Comment   |
|------------------|---|-------|---|--|---|
| Austin, 1995     | Kuopio, Finland<br>204 males and females                        | 65-74 | OGTT  | Tchol NS<br>HDLc NS<br>TG 2.3  | Cut-off levels not specified  |
| Charles, 1991    | Paris Prospective study<br>5042 men                             | 50-60 | OGTT  | TG NS  | Tchol not reported<br>HDLc not reported   |
| Chou, 1994       | Kinmen Islands,<br>Taiwan<br>3236 participants                  | > 30  | FPG 5.6-7.8<br>Then OGTT                                      | Tchol 1.5 (1.2-1.8)<br>HDLc 0.5 (0.3-1.0)<br>TG 1.5 (1.2-1.8)                      |   |
| Feskens, 1989    | Zutphen, Finland<br>841 males studied<br>again after 25 years   | 40-59 | Self reported<br>medically<br>confirmed<br>DM                 | Tchol 1.6 (0.9-2.9)  | HDLc not assessed<br>TG not assessed  |
| McPhillips, 1990 | Rancho Bernardo<br>study, US, 1847 people                       | 40-79 | FPG initial<br>OGTT at<br>follow up                           | Tchol 1.1 (0.8-1.3) M<br>1.2 (0.9-2.4) F<br>TG 1.2 (0.98-1.4) M<br>2.0 (1.6-2.6) F |   |
| Mykkanen, 1993   | Kuopio, Finland<br>892 males and females<br>Follow up 3.5 y     | 65-74 | OGTT  | HDLc < 1.0<br>2.1 (1.2-3.6)<br>TG > 2.5<br>2.7 (1.5-4.6)                           | For HDL < 1.0 and TG > 2.5 OR for ND 10.3 (4.0-27)  |
| Njolstad, 1998   | Finmark study,<br>Norway<br>11654 people<br>Follow up 12 y      | 35-52 | Questionnaire<br>& doctor or<br>medical<br>record<br>verified | Tchol NS<br>TG NS<br>HDLc – see<br>comment   | Lipids association but<br>expressed in increments<br>HDL < 1.0 v ≥ 1.5<br>significant only in females |
| Ohlson, 1988     | Gothenberg, Sweden<br>766 males<br>Follow up 13.5 y             | 54    | Self reported,<br>FPG and in<br>1980 OGTT<br>(100g)           | Tchol NS<br>TG NS  | HDLc not assessed   |
| Perry, 1995      | British Regional Heart<br>Study<br>7735 men<br>Follow up 12.8 y | 40-59 | RBG (≥11.1)<br>Questionnaire<br>only at follow<br>up          | Tchol NS<br>TG 2.8 (1.4-5.8)<br>HDLc 1.4 (0.8-2.6)                                 | Quintile levels not stated  |
| Shaten, 1993     | MRFIT study<br>6438 males                                       | 35-57 | OGTT<br>(1h PG only)  | LDLc NS<br>HDLc NS<br>TG NS  |   |
| Vanderpump, 1996 | Whickhan survey, UK<br>1877 survivors<br>Follow up 20 y         | > 18  | History of<br>diabetes or<br>elevated FPG                     | Tchol NS<br>TG 1.3M (0.8-2.3)<br>2.8 F(1.8-4.4)                                    | TG dichotomised at age<br>related 95 <sup>th</sup> centile but level<br>not stated                    |

ND=newly diagnosed; KDM=known diabetes; RPG=random plasma glucose; FPG=fasting plasma glucose;  
RBG=random blood glucose; OGTT=75g glucose and WHO criteria unless indicated;  
# - Odds ratio or relative risk (RR) unless otherwise stated

### **10. Use of risk factors assessment to identify undiagnosed diabetes**

Most people with undiagnosed Type 2 diabetes have easily identifiable risk factors (Cowie et al, 1994). Therefore, assessment of risk factors to identify people who might have undiagnosed Type 2 diabetes and who should be advised to undergo further testing is commonly advocated (Paterson, 1993; ADA, 2000). The use of risk factor assessment enables the population which should undergo further testing for undiagnosed Type 2 diabetes to be reduced with minimal effort.

The performance of such an approach has been assessed in relatively few studies. These studies have used different techniques to develop risk factor assessments. Study features which reduce their direct relevance to this guideline include – the inclusion of symptoms of diabetes (not considered in this guideline which focuses on the diagnosis of asymptomatic individuals), inclusion of different risk factors, proceeding straight from risk factor assessment to definitive testing with an OGTT (except for Barriga et al, 1996), and considering predictive values for IGT and diabetes combined (Barriga et al, 1996).

The ADA position statement recommends screening of all people with one or more risk factors or having symptoms of diabetes (ADA, 2000). The ADA (1993) has developed a questionnaire to numerically assess risk, however this questionnaire was not prospectively evaluated during its development (Herman et al, 1995). Burden et al (1994) did not find the questionnaire useful in community screening in the UK suggesting that a particular difficulty was the inclusion of non-specific symptoms (eg fatigue and blurred vision). More recently, Ruige et al (1997) tested this questionnaire in European populations and reported a sensitivity of 59%, specificity of 59% and positive predictive value (PPV) of 5.6% for identifying undiagnosed Type 2 diabetes.

Three studies (Herman et al, 1995; Ruige et al, 1997; Baan et al, 1999) have assessed risk stratification as a means of identifying people with undiagnosed Type 2 diabetes. Diabetes was defined by the OGTT in the whole of each population irrespective of risk status, and risk factors which most closely associated with diabetes were determined. The studies identified different sets of risk factors predictive of undiagnosed diabetes, although there were some commonalities. The outcome of the decision tree analysis used by Herman et al (1995) was the development of a proposed new simple modified questionnaire with the aim of detecting 5% undiagnosed Type 2 diabetes, similar to the overall objective used to develop the present guideline. Despite the differences in these studies, the three methods have similar performance in identifying people with undiagnosed Type 2 diabetes: sensitivity 72-78%, specificity 55-56% and PPV 6-8%.

The above studies evaluated their questionnaires only in terms of diabetes, but there may be additional benefits of recognising IGT and implementing interventions to either delay progression to overt diabetes and/or reduce the risk of a cardiovascular event. Barriga et al (1996) assessed their model for risk factors for predicting IGT and diabetes combined, including simultaneous measurement of fasting blood glucose. Using a combination of fasting blood glucose above 5.7 mmol/l and age above 62.5 years or BMI above 29.7, their model achieved a sensitivity of 93%, specificity of 55% and PPV of 31%. In contrast, a serial approach eliminated 35% from further testing using the criteria of age under 53.5 years and BMI less than 28 kgm<sup>-2</sup>. The remainder required a fasting blood glucose measurement of which 45% required an OGTT. This serial approach resulted in a sensitivity of 85% and a specificity of 64%.

With respect to the proportion of the population who would require further testing, the risk classification trees developed by Herman et al (1995), identified 30% of the population which needed follow up testing to establish a definitive diagnosis of diabetes. The method

developed by Ruige et al (1997), when applied in Caucasian people aged 45-74, identified 45% who would require definitive blood glucose testing in order to identify 72% with undiagnosed diabetes. Neither of these studies employed an intermediate step of measuring blood glucose between application of the risk factor questionnaire and performing an OGTT. The trade off with these risk factor assessment approaches compared with universal testing is that approximately 20% of undiagnosed diabetes will be missed but the need to unnecessarily test many people is avoided.

### **Summary – Risk factor assessment data**

- Risk factor assessment is a useful and commonly used method to identify people at increased risk of having undiagnosed Type 2 diabetes
- Risk factor assessment substantially reduces the number of people requiring testing for undiagnosed Type 2 diabetes
- Risk factor assessment achieves acceptable sensitivity, specificity and predictive values for detecting undiagnosed Type 2 diabetes

### **Comments – Who Should be Tested**

Since most people with undiagnosed Type 2 diabetes have easily recognisable risk factors, this approach is a useful first step in identifying people who should be further tested. This literature review has identified quantifiable risk factors which can be applied in a routine clinical setting with the aim of identifying groups of people with a 5% prevalence of undiagnosed Type 2 diabetes.

The review has confirmed some of the traditional risk factors such as impaired glucose tolerance (and impaired fasting glucose) and previous history of gestational diabetes. Age has been specified according to ethnicity in recognition of the younger age of development of Type 2 diabetes in Aboriginal and Torres Strait Islanders and peoples of certain non-English speaking backgrounds. Obesity, family history and hypertension have been combined with age 45 years and over. The increased risk of undiagnosed Type 2 diabetes in people with clinical cardiovascular disease is acknowledged and polycystic ovary syndrome has been added as a newly recognised risk factor.

Previous history of giving birth to a large baby, a factor traditionally included in diabetes risk factor lists, has been rejected on the basis of insufficient evidence. Other risk factors rejected through lack of evidence include smoking and blood lipid levels.

Although a well recognised risk factor associated with the future development of Type 2 diabetes, physical activity has not been included because of an inability to quantify risk against a clinically useful measure which could be applied in routine clinical practice.

## Evidence Table: Impaired Glucose Tolerance and Impaired Fasting Glucose

| Author   | Evidence          |                 |                |                     |                  |
|--|-------------------|-----------------|----------------|---------------------|------------------|
|  | Level of evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|  | Level             | Study Type      |                |                     |                  |
| <b>Charles MA (1991)</b><br>(Adult men – France)                                     | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Chou P (1998)</b><br>(Adults – Kinmen Islands, Taiwan)                            | III-2             | Cohort          | High           | High <sup>+</sup>   | Medium           |
| <b>Edelstein SL (1997)</b><br>(Adults – US; Nauru)                                   | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Haffner SM (1997)</b><br>(Adults – US: Mexican Americans and Non-Hispanic Whites) | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Motala AA (1993)</b><br>(Adolescents & Adults - South African Indians)            | III-2             | Cohort          | Medium         | High <sup>+</sup>   | Medium           |
| <b>Mykkanen L (1993)</b><br>(Elderly – Finland)                                      | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Nijpels G (1997)</b><br>(Adults – Netherlands)                                    | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Pan X-R (1997)</b><br>(Adults – China)  | II                | RCT             | High           | High <sup>+</sup>   | Medium           |
| <b>Qureshi AI (1998)</b><br>(Adults – US)  | III-2             | Cross-sectional | High           | Low                 | High             |
| <b>Ramachandran A (1986)</b><br>(Adults – India)                                     | III-2             | Cohort          | High           | High <sup>+</sup>   | Medium           |
| <b>Saad MF (1988)</b><br>(5 years and older – US: Pima Indians)                      | III-2             | Cohort          | High           | High <sup>+</sup>   | Low              |
| <b>Schranz AG (1989)</b><br>(Adults – Malta)   | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Shaw JE (1999a)</b><br>(Adults – Mauritius)                                       | III-2             | Cohort          | High           | High <sup>+</sup>   | Low              |
| <b>Stengard J H (1993)</b><br>(Elderly men - Finland)                                | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Swai ABM (1990)</b><br>(Adolescents & adults – Tanzania)                          | III-2             | Cross-sectional | High           | Medium <sup>+</sup> | Low              |
| <b>Tukuitonga CF (1990)</b><br>(Adults – Niue)                                       | III-2             | Cohort          | High           | High <sup>+</sup>   | Medium           |
| <b>Vaccaro O (1999)</b><br>(Adults – Italy)  | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |

<sup>+</sup> People in these groups are at increased risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect. Low = no statistically significant effect

## Evidence Table: History of Gestational Diabetes Mellitus

| Author   | Evidence          |              |                |                     |                  |
|--|-------------------|--------------|----------------|---------------------|------------------|
|  | Level of Evidence |              | Quality Rating | Magnitude Rating    | Relevance Rating |
|  | Level             | Study Type   |                |                     |                  |
| <b>Benjamin E (1993)</b><br>(Adult women - US: Zuni Indians)     | III-2             | Case-control | High           | High <sup>+</sup>   | Low              |
| <b>Damm P (1989)</b><br>(Adult women - Denmark)                  | III-2             | Case-control | High           | High <sup>+</sup>   | High             |
| <b>Hanson U (1996)</b><br>(Adult women - Sweden)                 | III-2             | Cohort       | High           | High <sup>-</sup>   | High             |
| <b>Henry OA (1991)</b><br>(Adult women - Australia)              | III-2             | Cohort       | High           | Medium <sup>+</sup> | High             |
| <b>McGuire V (1996)</b><br>(Adult women - US)                    | III-2             | Case-control | Medium         | High <sup>+</sup>   | High             |
| <b>Metzger BE (1993)</b><br>(Adult women - US)                   | III-2             | Cohort       | High           | High <sup>+</sup>   | High             |
| <b>O' Sullivan JB (1989)</b><br>(Adult women - US)               | III-2             | Case-control | High           | High <sup>+</sup>   | High             |
| <b>Persson B (1991)</b><br>(Adult women - Sweden)                | III-2             | Case-control | High           | High <sup>+</sup>   | High             |
| <b>Peters RK (1996)</b><br>(Adult women - US: Latino)            | III-2             | Cohort       | High           | High <sup>+</sup>   | Low              |
| <b>Steinhart JR (1997)</b><br>(Adult women - US: Navajo Indians) | III-2             | Cohort       | High           | High <sup>+</sup>   | Low              |

<sup>+</sup> People with a history of GDM are at increased risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by '+' for a positive effect and '-' for a negative effect.

## Evidence Table: Age – Caucasian Populations

| Author  | Evidence          |                 |                |                     |                  |
|---|-------------------|-----------------|----------------|---------------------|------------------|
|   | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|   | Level             | Study Type      |                |                     |                  |
| <b>Costa A (1998)</b><br>(Adults – Spain)                                 | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Forrest RD (1986)</b><br>(Adults - UK)                                 | III-2             | Cross-sectional | High           | Medium <sup>+</sup> | High             |
| <b>Garancini MP (1995)</b><br>(Adults - Italy)                            | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Glatthaar C (1985)</b><br>(Adults – Australia)                         | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Guest CS (1992)</b><br>(Australia: Europids and Australian Aborigines) | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Harris MI (1987)</b><br>(Adults - US)                                  | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Harris MI (1998)</b><br>(Adults - US)                                  | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Mitchell P (1998)</b><br>(Elderly - Australia)                         | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Mooy JM (1995)</b><br>(Adults – The Netherlands)                       | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Simmons D (1991)</b><br>(Adults - UK: Europids, Asians)                | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Stolk RP (1997)</b><br>(Adults - The Netherlands)                      | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Tuomileho J (1991)</b><br>(Middle-aged Adults – Finland)               | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Welborn TA (1989)</b><br>(Adults - Australia)                          | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Welborn TA (1997)</b><br>(Adults - Australia)                          | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Yudkin JS (1993)</b><br>(Adults – UK)                                  | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Zimmet PZ (2000)</b><br>(Adults – Australia)                           | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |

<sup>+</sup> In a Caucasian population age increases the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Evidence Table: Age – Aborigines & Torres Strait Islanders

| Author  | Evidence          |                   |                |                   |                  |
|---|-------------------|-------------------|----------------|-------------------|------------------|
|   | Level of Evidence |                   | Quality Rating | Magnitude Rating  | Relevance Rating |
|   | Level             | Study Type        |                |                   |                  |
| <b>Bastian P (1979)</b><br>(Adults – West Kimberley, Australia: Aborigines)     | III-2             | Cross-sectional   | Medium         | High <sup>+</sup> | High             |
| <b>Braun B (1996)</b><br>(Children – Australian Aborigines)                     | III-2             | Cohort            | Medium         | High <sup>+</sup> | High             |
| <b>Cameron WI (1986)</b><br>(Adults – Bourke, Australia: Aborigines)            | III-2             | Cross-sectional   | Medium         | High <sup>+</sup> | High             |
| <b>Colagiuri S (1999a)</b><br>(Adults – NSW, Australia: Aborigines)             | III-2             | Cross-sectional   | High           | High <sup>+</sup> | High             |
| <b>de Courten M (1998)</b><br>(Aboriginal & Torres Strait Islander populations) | I                 | Systematic review | High           | High <sup>+</sup> | High             |
| <b>Guest CS (1992)</b><br>(Adults - SE Australia: Europids, Aborigines)         | III-2             | Case control      | Medium         | High <sup>+</sup> | High             |
| <b>O'Dea K (1982)</b><br>(Adult & Adolescent men – Australia: Aborigines)       | III-2             | Case control      | High           | High <sup>+</sup> | High             |
| <b>O'Dea K (1988)</b><br>(Adults – Desert, Australia: Aborigines)               | III-2             | Cross-sectional   | High           | High <sup>+</sup> | High             |
| <b>O'Dea K (1990)</b><br>(Adults – Northern Australia: Aborigines)              | III-2             | Cross-sectional   | High           | High <sup>+</sup> | High             |
| <b>O'Dea K (1993)</b><br>(Adults – Northern Australia: Aborigines)              | III-2             | Cross-sectional   | High           | High <sup>+</sup> | High             |

<sup>+</sup> In the Aboriginal & Torres Strait Islander population age increases the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Evidence Table: Age – Non-English Speaking Background People

| Author   | Evidence          |                 |                |                   |                  |
|--|-------------------|-----------------|----------------|-------------------|------------------|
|  | Level of Evidence |                 | Quality Rating | Magnitude Rating  | Relevance Rating |
|  | Level             | Study Type      |                |                   |                  |
| <b>Amini M (1997)</b><br>(Adults - Iran)                                     | III-2             | Cross-sectional | Medium         | High <sup>+</sup> | Medium           |
| <b>Asfour MG (1995)</b><br>(Adults - Sultanate of Oman)                      | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |
| <b>Cockram CS (1993)</b><br>(Adults - Hong Kong: Chinese)                    | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |
| <b>Colagiuri S (1999b)</b><br>(Adults - Tonga)                               | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |
| <b>Dowse GK (1990)</b><br>(Adults – Mauritius)                               | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |
| <b>Lu F-H (1998)</b><br>(Adults - Taiwan)                                    | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |
| <b>Omar MAK (1994)</b><br>(Adults - South Africa: Indians)                   | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |
| <b>Ramachandran A (1992)</b><br>(Adults - India)                             | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |
| <b>Shera AS (1995)</b><br>(Adults - Pakistan)                                | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |
| <b>Simmons D (1991)</b><br>(Adults - UK: Europids, Asians)                   | III-2             | Cross-sectional | High           | High <sup>+</sup> | High             |
| <b>Tan CE (1999)</b><br>(Adults – Singapore: Chinese, Malays, Asian Indians) | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |
| <b>Unwin N (1997)</b><br>(Adults – UK: Europids, Chinese)                    | III-2             | Cross-sectional | High           | High <sup>+</sup> | High             |
| <b>Zimmet PZ (1999b)</b><br>(Adults – Nauru)                                 | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |

<sup>+</sup> In those from a Non English speaking background age increases the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Evidence Table: Obesity

| Author  | Evidence          |                 |                |                     |                  |
|---|-------------------|-----------------|----------------|---------------------|------------------|
|   | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|   | Level             | Study Type      |                |                     |                  |
| <b>Baan CA (1999)</b><br>(Adults – The Netherlands)                   | III-2             | Cross-sectional | High           | Medium <sup>+</sup> | High             |
| <b>Carey VJ (1997)</b><br>(Adult women - US)                          | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Cassano PA (1992)</b><br>(Adult men – US)                          | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Chan JM (1994)</b><br>(Adult men - US)                             | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Chou P (1994)</b><br>(Adults –Kinmen Islands, Taiwan)              | III-2             | Cross-sectional | High           | High <sup>+</sup>   | Medium           |
| <b>Colditz GA (1990)</b><br>(Adult women - US)                        | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Colditz GA (1995)</b><br>(Adult women - US)                        | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Everhart JE (1992)</b><br>(Adults & Adolescents- US: Pima Indians) | III-2             | Cohort          | High           | High <sup>+</sup>   | Low              |
| <b>Feskens EJM (1989)</b><br>(Adult men – The Netherlands)            | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Ford ES (1997)</b><br>(Adults – US)                                | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Gurwitz JH (1994)</b><br>(Elderly – US)                            | III-2             | Cohort          | High           | Medium <sup>+</sup> | High             |
| <b>Hanson RL (1995)</b><br>(Adults – US: Pima Indians)                | III-2             | Cohort          | High           | Medium <sup>+</sup> | Low              |
| <b>Harris MI (1987)</b><br>(Adults – US)                              | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Holbrook TL (1990)</b><br>(Adult - US)                             | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Modan M (1986)</b><br>(Adults – Israel)                            | III-2             | Cohort          | High           | High <sup>+</sup>   | Medium           |
| <b>Njolstad I (1998)</b><br>(Adults – Norway)                         | III-2             | Cohort          | High           | Medium <sup>+</sup> | High             |
| <b>Perry IJ (1995)</b><br>(Adult men - UK)                            | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Resnick HE (1998)</b><br>(Adults – US)                             | III-2             | Cohort          | Medium         | High <sup>+</sup>   | High             |
| <b>Ruige JB (1997)</b><br>(Adults – The Netherlands)                  | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Sakurai Y (1999)</b><br>(Adult men - Japan)                        | III-2             | Case control    | High           | High <sup>+</sup>   | Low              |
| <b>Shaper AG (1997)</b><br>(Adult men – UK)                           | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Shaten BJ (1993)</b><br>(Adult men – US)                           | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Vanderpump MPJ (1996)</b><br>(Adults – UK)                         | III-2             | Cohort          | High           | Medium <sup>+</sup> | High             |
| <b>Welborn TA (1997)</b><br>(Adults – Australia)                      | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |

<sup>+</sup> Obesity increases the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Evidence Table: Family History

| Author   | Evidence          |                 |                |                     |                  |
|--|-------------------|-----------------|----------------|---------------------|------------------|
|  | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|  | Level             | Study Type      |                |                     |                  |
| <b>Boer JM (1996)</b><br>(Elderly men – The Netherlands)                           | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Chan JM (1994)</b><br>(Adult men - US)  | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Costa A (1998)</b><br>(Adults - Spain)  | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Grill V (1999)</b><br>(Adult men - Sweden)                                      | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Groop L (1996)</b><br>(Adults – Finland)  | III-2             | Case control    | High           | High <sup>+</sup>   | High             |
| <b>Harris MI (1987)</b><br>(Adults - US)   | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Kawakami N (1997)</b><br>(Adult men - Japan)                                    | III-2             | Cohort          | High           | High <sup>+</sup>   | Low              |
| <b>Kekalainen P (1999)</b><br>(Adults - Finland)                                   | III-2             | Case control    | High           | High <sup>+</sup>   | High             |
| <b>Mitchell BD (1993)</b><br>(Adults - US: Mexican Americans, Non-Hispanic Whites) | III-2             | Cross-sectional | High           | Medium <sup>+</sup> | High             |
| <b>Mooy JM (1995)</b><br>(Adults – The Netherlands)                                | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Mykkanen L (1990)</b><br>(Elderly - Finland)                                    | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Ohlson LO (1988)</b><br>(Adult men - Sweden)                                    | III-2             | Cohort          | High           | High                | High             |
| <b>Ruige JB (1997)</b><br>(Adults – The Netherlands)                               | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Shaten BJ (1993)</b><br>(Adult men - US)  | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Sugimori H (1998)</b><br>(Adults – Japan)                                       | III-2             | Cohort          | High           | Medium <sup>+</sup> | Low              |
| <b>Todoroki I (1994)</b><br>(Adult men - Japan)                                    | III-2             | Cross-sectional | High           | High <sup>+</sup>   | Low              |
| <b>Welborn TA (1997)</b><br>(Adults – Australia)                                   | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |

<sup>+</sup> A family history of diabetes increases the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Evidence Table: Hypertension

| Author  | Evidence          |                 |                |                     |                  |
|---|-------------------|-----------------|----------------|---------------------|------------------|
|   | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|   | Level             | Study Type      |                |                     |                  |
| <b>Baan CA (1999)</b><br>(Adults – The Netherlands)                   | III-2             | Cross-sectional | High           | Medium <sup>+</sup> | High             |
| <b>Bog-Hansen E (1998)</b><br>(Adults – Sweden)                       | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Chou P (1994)</b><br>(Adults – Kinmen islands, Taiwan)             | III-2             | Cross-sectional | High           | High <sup>+</sup>   | Medium           |
| <b>Feskens EJM (1995)</b><br>(Elderly men – Finland; The Netherlands) | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Gurwitz JH (1992)</b><br>(Adults – US)                             | III-2             | Case-control    | High           | Medium <sup>+</sup> | High             |
| <b>Hayashi T (1999)</b><br>(Adult men – Japan)                        | III-2             | Cohort          | High           | High <sup>+</sup>   | Low              |
| <b>Helmrich SP (1991)</b><br>(Adult men – US)                         | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Mykkanen L (1994)</b><br>(Elderly – Finland)                       | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Ruige JB (1997)</b><br>(Adults – The Netherlands)                  | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Saad MF (1990)</b><br>(Adult – US: Pima Indians)                   | III-2             | Cross-sectional | High           | High <sup>+</sup>   | Low              |
| <b>Sugimori H (1998)</b><br>(Adults – Japan)                          | III-2             | Cohort          | High           | High <sup>+</sup>   | Low              |
| <b>Vanderpump MPJ (1996)</b><br>(Adults – UK)                         | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Welborn TA (1997)</b><br>(Adults – Australia)                      | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |

<sup>+</sup> The presence of hypertension increases the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Evidence Table: Cardiovascular Disease

| Author  | Evidence          |                 |                |                     |                  |
|---|-------------------|-----------------|----------------|---------------------|------------------|
|   | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|   | Level             | Study Type      |                |                     |                  |
| <b>Farrer M (1995)</b><br>(Adults – UK)       | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Gray CS (1987)</b><br>(Adults – UK)        | III-2             | Cohort          | Medium         | High <sup>+</sup>   | High             |
| <b>Katz R (1994)</b><br>(Adults – US)         | III-2             | Cross-sectional | Medium         | Medium <sup>+</sup> | High             |
| <b>Madsen JK (1986)</b><br>(Adults – Denmark) | III-2             | Cross-sectional | Medium         | Medium <sup>-</sup> | High             |
| <b>Oppenheimer SM (1985)</b><br>(Adults – UK) | III-2             | Cohort          | Medium         | High <sup>+</sup>   | High             |
| <b>Oswald GA (1984)</b><br>(Adults – UK)      | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Riddle MC (1982)</b><br>(Adults – UK)      | III-2             | Case-control    | High           | Medium <sup>+</sup> | High             |

<sup>+</sup> The presence of cardiovascular disease increases the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Evidence Table: Polycystic Ovary Syndrome

| Author   | Evidence          |              |                |                     |                  |
|--|-------------------|--------------|----------------|---------------------|------------------|
|  | Level of Evidence |              | Quality Rating | Magnitude Rating    | Relevance Rating |
|  | Level             | Study Type   |                |                     |                  |
| <b>Dahlgren E (1992)</b><br>(Adult women - Sweden) | III-2             | Case-control | Medium         | High <sup>+</sup>   | High             |
| <b>Ehrmann DA (1996)</b><br>(Adult women - US)     | III-2             | Cohort       | High           | High <sup>+</sup>   | High             |
| <b>Legro RS (1999)</b><br>(Adult women - US)       | III-2             | Case-control | High           | High <sup>+</sup>   | High             |
| <b>Wild Sh (1998)</b><br>(Adult women - UK)        | III-2             | Case-control | Low            | Medium <sup>+</sup> | High             |

<sup>+</sup> The presence of polycystic ovary syndrome increases the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by '+' for a positive effect and '-' for a negative effect.

## Evidence Table: Smoking

| Author   | Evidence          |                 |                |                     |                  |
|--|-------------------|-----------------|----------------|---------------------|------------------|
|  | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|  | Level             | Study Type      |                |                     |                  |
| <b>Cassano PA (1992)</b><br>(Adult men – US)                           | III-2             | Cohort          | Medium         | Low                 | High             |
| <b>Feskens EJM (1989)</b><br>(Adult men – The Netherlands)             | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Fujimoto WY (1990)</b><br>(Adults - US: Japanese American)          | III-2             | Cross-sectional | High           | Low                 | Low              |
| <b>Kawakami N (1997)</b><br>(Adult men – Japan)                        | III-2             | Cohort          | High           | High <sup>+</sup>   | Low              |
| <b>Mooy JM (1995)</b><br>(Adults – The Netherlands)                    | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Njolstad I (1998)</b><br>(Adults – Norway)                          | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Ohlson L-O (1988)</b><br>(Adult men – Sweden)                       | III-2             | Cohort          | High           | Low                 | High             |
| <b>Perry IJ (1995)</b><br>(Adult men – UK)                             | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Qiao Q (1999)</b><br>(Adult men – Finland)                          | III-2             | Cohort          | High           | Medium <sup>+</sup> | High             |
| <b>Rimm EB (1993)</b><br>(Adult women – US)                            | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Rimm EB (1995)</b><br>(Adult men – US)                              | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Rodriguez BL (1996)</b><br>(Elderly men – Hawaii: Japanese descent) | III-2             | Cross-sectional | High           | Low                 | Low              |
| <b>Shaten BJ (1993)</b><br>(Adult men – US)                            | III-2             | Cohort          | Medium         | Medium <sup>+</sup> | High             |
| <b>Sugimori H (1998)</b><br>(Adults – Japan)                           | III-2             | Cohort          | Medium         | Low                 | Low              |
| <b>Todoroki I (1994)</b><br>(Adult men – Japan)                        | III-2             | Cross-sectional | High           | High <sup>+</sup>   | Low              |
| <b>Uchimoto S (1999)</b><br>(Adult men – Japan)                        | III-2             | Cohort          | High           | High <sup>+</sup>   | Low              |

<sup>+</sup> Smoking increases the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect. Low = no statistically significant effect

## Evidence Table: Giving Birth to a Large Baby

| Author   | Evidence          |                 |                |                     |                  |
|--|-------------------|-----------------|----------------|---------------------|------------------|
|  | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|  | Level             | Study Type      |                |                     |                  |
| <b>Cowie CC (1995)</b><br>(Adult women – US)         | III-2             | Cross-sectional | High           | Medium <sup>+</sup> | High             |
| <b>Herman WH (1995)</b><br>(Adults - US)             | III-2             | Cross-sectional | Medium         | Medium <sup>+</sup> | High             |
| <b>Larsson G (1986)</b><br>(Adult women - Sweden)    | III-2             | Case control    | High           | Medium <sup>+</sup> | High             |
| <b>McGuire V (1996)</b><br>(Adult women - US)        | III-2             | Case control    | Medium         | High <sup>+</sup>   | High             |
| <b>O'Sullivan JB (1980)</b><br>(Adult women - US)    | III-2             | Case control    | High           | Low                 | High             |
| <b>Ruige JB (1997)</b><br>(Adults – The Netherlands) | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |

<sup>+</sup> Giving birth to a large baby increases the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect. Low = no statistically significant effect

## Evidence Table: Lipids

| Author   | Evidence          |                 |                |                   |                  |
|--|-------------------|-----------------|----------------|-------------------|------------------|
|  | Level of Evidence |                 | Quality Rating | Magnitude Rating  | Relevance Rating |
|  | Level             | Study Type      |                |                   |                  |
| <b>Austin MA (1995)</b><br>(Elderly – Finland)             | III-2             | Case-control    | High           | Low               | High             |
| <b>Charles MA (1991)</b><br>(Adult men – France)           | III-2             | Cohort          | High           | Low               | High             |
| <b>Chou P (1994)</b><br>(Adults- Kinmen Islands, Taiwan)   | III-2             | Cross-sectional | High           | High <sup>+</sup> | Medium           |
| <b>Feskens EJM (1989)</b><br>(Adult men – The Netherlands) | III-2             | Cohort          | High           | High <sup>+</sup> | High             |
| <b>McPhillips JB (1990)</b><br>(Adults – US)               | III-2             | Cohort          | High           | High <sup>+</sup> | High             |
| <b>Mykkanen L (1993)</b><br>(Elderly – Finland)            | III-2             | Cohort          | High           | High <sup>+</sup> | High             |
| <b>Njolstad I (1998)</b><br>(Adults – Norway)              | III-2             | Cohort          | High           | High <sup>+</sup> | High             |
| <b>Ohlson LO (1988)</b><br>(Adult men - Sweden)            | III-2             | Cohort          | High           | High <sup>+</sup> | High             |
| <b>Perry IJ (1995)</b><br>(Adult men - UK)                 | III-2             | Cohort          | High           | High <sup>+</sup> | High             |
| <b>Shaten BJ (1993)</b><br>(Adult men – US)                | III-2             | Cohort          | High           | High <sup>+</sup> | High             |
| <b>Vanderpump MPJ (1996)</b><br>(Adults – UK)              | III-2             | Cohort          | Medium         | High <sup>+</sup> | High             |

<sup>+</sup> Altered lipid levels increase the risk of developing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect. Low = no statistically significant effect

## Evidence Table: Risk Factor Assessment

| Author  | Evidence          |                 |                |                     |                  |
|---|-------------------|-----------------|----------------|---------------------|------------------|
|   | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|   | Level             | Study Type      |                |                     |                  |
| <b>Baan CA (1999)</b><br>(Adult men – The Netherlands)                              | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Barriga KJ (1996)</b><br>(Adults – US: Hispanics & non-Hispanic whites)          | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Herman WH (1995)</b><br>(Adults – US: white, black, Hispanic & native Americans) | III-2             | Cross-sectional | Medium         | Medium <sup>+</sup> | High             |
| <b>Ruige JB (1997)</b><br>(Adults – The Netherlands)                                | III-2             | Cross-sectional | High           | High <sup>+</sup>   | High             |

<sup>+</sup> Risk factor assessment increases the risk of detecting the development of Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Section 3: Case Detection and Diagnosis

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### Issue

**How should case detection and diagnostic testing for Type 2 diabetes be performed?**

### Recommendations

Fasting plasma glucose should be measured as the initial screening test in people with risk factors for undiagnosed Type 2 diabetes.

A random plasma glucose may be used if collection of a fasting sample is considered impractical.

Laboratory testing (rather than blood glucose meter testing) should be used to measure blood glucose for the screening test.

Laboratory testing is mandatory for the diagnostic test.

The 1999 WHO criteria should be used to diagnose Type 2 diabetes.

An oral glucose tolerance test should be performed in all people with an equivocal result – fasting plasma glucose of 5.5-6.9 mmol/l, or random plasma glucose of 5.5-11.0 mmol/l.

The diagnosis of diabetes requires two positive laboratory blood tests on separate days unless the plasma glucose is unequivocally elevated in the presence of acute metabolic decompensation or obvious symptoms.

### Evidence statements

- Fasting plasma glucose has the highest sensitivity and specificity for screening for undiagnosed Type 2 diabetes  
*Evidence Level III<sup>#</sup>*
- A screening blood glucose level of less than 5.5 mmol/l is associated with a low chance of undiagnosed Type 2 diabetes  
*Evidence Level III<sup>#</sup>*

## Evidence statements continued

- Blood glucose meters lack sufficient accuracy for screening for undiagnosed Type 2 diabetes  
*Evidence Level III<sup>#</sup>*
- Isolated abnormalities of 2 hour plasma glucose values during an oral glucose tolerance test are common and are associated with increased mortality  
*Evidence Level III<sup>#</sup>*
- The WHO 1999 criteria provide the best opportunity to detect individuals with abnormalities of either fasting and/or post glucose load plasma glucose levels –  
*Evidence Level III<sup>#</sup>*

## Background – How to Detect Type 2 Diabetes

Changes have recently been made to the classification and diagnostic criteria for diabetes which have been endorsed by international groups including the World Health Organization (WHO, 1999), the American Diabetes Association (ADA, 1997) and the Australian Diabetes Society (Colman et al, 1999).

The new classification of diabetes includes 4 main categories: Type 1 diabetes, Type 2 diabetes, other specific types and gestational diabetes. This classification and nomenclature moves away from inferences related to treatment modality. Two other abnormalities of glucose tolerance intermediate between normality and diabetes are defined – impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). IGT and IFG are stages in the natural history of disordered carbohydrate metabolism rather than a subclass of diabetes. They are not considered as clinical entities in their own right (except during pregnancy) but rather are risk factors for the future development of diabetes and cardiovascular disease (ADA, 1997; WHO, 1999).

The new diagnostic criteria for diabetes are shown in Table 13 and the values for other blood sampling methods are shown in Appendix 1. The main changes from the previous classification and diagnostic criteria relate to the fasting threshold for diabetes (lowered from 7.8 to 7.0 mmol/l) and the introduction of the IFG category for fasting plasma glucose levels of 6.1 to 6.9 mmol/l.

Plasma glucose concentrations are distributed over a continuum but there is an approximate threshold separating those who are at a substantially increased risk for adverse outcomes caused by diabetes (eg microvascular complications) from those who are not. The ADA (1997) chose a plasma glucose level of 6.0 mmol/l as the upper limit of normal because it is the level above which acute phase insulin secretion is lost in response to intravenous administration of glucose and it is associated with a progressively greater risk of developing microvascular and macrovascular complications.

The fasting plasma glucose level for diagnosing diabetes has been reduced to 7.0 mmol/l in recognition of the association of this level and the increased risk of retinopathy and because this level corresponds more closely with a 2-hour post glucose level of 11.1 mmol/l compared with the previous threshold value of 7.8 mmol/l (reviewed in ADA 1997). Finch et al (1990a) were the first to suggest that a fasting plasma glucose of 7 mmol/l corresponded better to a 2-hour post glucose level in diagnosing diabetes for prevalence surveys compared with a fasting plasma glucose of 7.8 mmol/l.

Two areas of difference between the WHO and ADA recommendations remain. Firstly, the use of the oral glucose tolerance test (OGTT) which continues to be recommended by WHO for all people with equivocal results whereas the ADA suggests that the OGTT is rarely necessary in the diagnostic algorithm, except in pregnancy. The Australian Diabetes Society has followed the WHO position on this point (Colman et al, 1999). Secondly, recommendations for screening and diagnosis of gestational diabetes differ. The ADA recommends selective screening and a 100g 3-hour OGTT interpreted by National Diabetes Diagnostic Criteria (NDDG) values for gestational diabetes (ADA, 1997), whereas WHO recommends using the 75g 2-hour OGTT interpreted according to the criteria used in non-pregnant adults (WHO, 1999).

The diagnosis of diabetes can be made in 3 ways but each must be confirmed on a subsequent day unless unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms are present:

- a) Symptoms of diabetes and casual plasma glucose  $\geq 11.1$  mmol/l (casual means any time of day regardless of time of last meal)
- b) Fasting plasma glucose  $\geq 7.0$  mmol/l
- c) 2-hour plasma glucose  $\geq 11.1$  mmol/l during an OGTT

**Table 13: Values for diagnosis\* of diabetes and other categories of hyperglycaemia**

|                                    | Plasma glucose concentration<br>(mmol/l) |
|------------------------------------|--|
| <b>Diabetes Mellitus:</b>          |  |
| Fasting                            | $\geq 7.0$                               |
| <i>or</i>                          |  |
| 2-h post glucose load              | $\geq 11.1$                              |
| <b>Impaired Glucose Tolerance:</b> |  |
| Fasting                            | $< 7.0$                                  |
| <i>and</i>                         |  |
| 2-h post glucose load              | $\geq 7.8$ and $< 11.1$                  |
| <b>Impaired Fasting Glucose:</b>   |  |
| Fasting                            | $\geq 6.1$ and $< 7.0$                   |
| 2-h (if measured)                  | $< 7.8$                                  |

\* Note that diabetes can only be diagnosed in an individual when these diagnostic values are confirmed on another day

## Evidence – How to Detect Type 2 Diabetes

### The Initial Screening Test

The prevalence rates of undiagnosed Type 2 diabetes in most populations do not warrant universal testing. Having identified at risk individuals, the options are to proceed directly to definitive testing for diabetes or use an intermediate screening test to exclude people with a low chance of having diabetes and to identify people who require further testing. A number of different screening tests have been used. An important consideration is that assessment of performance of the different methods has invariably been evaluated in population studies which examine their effect in terms of overall diabetes prevalence, whereas these guidelines relate to the detection of *individuals* with undiagnosed Type 2 diabetes.

There are several considerations in attempting to define an appropriate screening test. Case detection and diagnosis are based on some degree of hyperglycaemia but it is important to remember that this requires criteria which involve dichotomisation of a continuous variable. The separation of normal from abnormal is inevitably arbitrary and this invariably results in a less than perfect correlation between the screening and diagnostic tests.

The characteristics of tests for population screening for case finding and diagnosis of undiagnosed Type 2 diabetes have been considered by many authors. The overall purpose of the screening test is to identify as many individuals as possible who require further testing because they may have diabetes, and to identify people in whom the diagnosis is unlikely and therefore should not be subjected to unnecessary further testing. Wiener (1998) proposes that for this purpose, the test should pick up as many true positives as possible at the risk of including some false positives who could be eliminated by latter testing – ie the test should have a high sensitivity but specificity is not quite as important.

Vinacor (1999) argues that establishing a diagnosis is perhaps the most important component of medical care and that the balance between sensitivity and specificity should be determined by the perceived benefits and risks of the available treatment. Because the effectiveness of treatment of diabetes was questioned in the 70's and 80's, specificity of plasma glucose cut points was emphasised. However, with emergence of the beneficial effects of blood glucose control in the 1990's, criteria which are more sensitive, but less specific, have been adopted.

Ultimately the choice of test will depend not only on the characteristics of the test but also on the circumstances under which it is being performed, confidence in the compliance of the individual being tested and on availability and affordability of the different methods.

#### **1. Fasting plasma glucose**

Measurement of fasting plasma glucose (FPG) is a relatively simple procedure which can often be combined with pathology testing for other reasons. The usefulness of particular levels of FPG in predicting undiagnosed diabetes has been assessed in several studies. Most have focused on a FPG  $\geq 6.1$  mmol/l, being the new cutoff point between normal and abnormal proposed by the ADA (1997). However, another relevant FPG level is 5.5 mmol/l, being the WHO cut point below which the diagnosis of diabetes is unlikely (WHO, 1999).

A FPG level of approximately 5.5 mmol/l as the cutoff point defining low risk of undiagnosed Type 2 diabetes is supported by a number of studies. Costa et al (1999) examined FPG results in 616 non-diabetic bank employees being tested with an OGTT and reported that an FPG  $\geq 5.4$  mmol/l achieved optimal sensitivity and specificity. Below this level 0.5% had undiagnosed diabetes and 3.2% IGT compared with 4% diabetes and 21% IGT above this cutoff point. Borthey et al (1994) reported that the best equilibrium between

sensitivity and specificity for the diagnosis of diabetes was achieved at a cutoff of 5.6 mmol/l for fasting capillary blood glucose in their study of 4 019 Brazilian people undergoing an OGTT. The DECODE Study Group (DECODE, 1999b) analysed data from many European studies which included a total of 29 108 people who had an OGTT. Using an FPG cutoff point of > 5.5 mmol/l would identify 93% of people with diabetes and 69% of people with IGT. By comparison a cutoff for FPG of 6.1-6.9 mmol/l would identify 82% of people with diabetes and 29% of those with IGT. Larsson et al (1995) reported that optimal sensitivity and specificity for detecting undiagnosed diabetes was achieved in their cohort of women aged 55-57 years with a fasting blood glucose of 5.3 mmol/l. – sensitivity and specificity were 77% and PPV 11.9%. Wiener (1995) found similar results in a small group of non-pregnant adults undergoing OGTT with a FPG of 5.5 mmol/l having a sensitivity of 89% and specificity of 59%. Cockram et al (1992) reported that a FPG of 5.6 mmol/l gave a sensitivity and specificity of 87% compared with a 2-hour plasma glucose of 11.1 mmol/l.

Two recent short reports from Australia presented data on individuals referred for OGTT for different categories of glucose tolerance according to FPG which included a 5.5 mmol/l cutoff value (Appleton et al, 1999; Diamond & Meerkin, 1999) (Table 14). Approximately twice as many people with FPG between 5.5 and 6.0 mmol/l had diabetes and IGT compared with people with FPG values below 5.5 mmol/l. Similarly, Ramachandran et al (1993) reported that only 1% of people with an FPG below 5.5 mmol/l had diabetes in an Asian Indian population from South India.

**Table 14: The performance of various levels of fasting plasma glucose in detecting abnormalities of glucose tolerance**

| Reference      | N     | FPG < 5.5 mmol/l |     |     |    | FPG 5.5-6.0 mmol/l |     |     |     | FPG 6.1-6.9 |     |     |     |
|----------------|-------|------------------|-----|-----|----|--------------------|-----|-----|-----|-------------|-----|-----|-----|
|                |       | Total            | NGT | IGT | DM | Total              | NGT | IGT | DM  | Total       | NGT | IGT | DM  |
| Appleton, 1999 | 44592 | 31%              | 77% | 19% | 3% | 30%                | 67% | 26% | 7%  | 23%         | 39% | 39% | 22% |
| Diamond, 1999  | 2341  | 53%              | 73% | 23% | 4% | 20%                | 49% | 40% | 11% | 16%         | 22% | 34% | 44% |

NGT = normal glucose tolerance; IGT = impaired glucose tolerance; DM = diabetes mellitus

Total = % of total population within each plasma glucose range

% for NGT, IGT, DM within each plasma glucose range refer to % of total in that range

Modan and Harris (1994) compared the performance of various FPG levels in people in the USA and Israel for detecting undiagnosed Type 2 diabetes. Thirty five percent of people in the USA and 19% of people from Israel with newly diagnosed diabetes had an FPG less than 6.1 mmol/l. While these authors concluded that no FPG level provided a satisfactory cutoff point to use in screening for undiagnosed diabetes, an FPG of  $\geq 5.55$  mmol/l was more effective than other FPG levels. This level had a sensitivity of 83% and 95% respectively in the USA and Israel with corresponding specificities of 76% and 47%, and PPVs of 17.2% and 11.8%. Davies et al (1993) performed a similar study in 442 people from the Isle of Ely, UK. At a FPG cutoff of 5.5 mmol/l sensitivity was 96% and specificity 28%, compared with results of 65% and 64% respectively with a cutoff of 6 mmol/l.

A number of studies have reported on the properties of an FPG of 6.1 mmol/l and above as a screening tool for diabetes but did not include results of values below this level. These studies from different populations report sensitivities ranging from 58-87% (median – 81%) and specificities ranging from 75-98% (median 92%) (Harris et al, 1997; Chang et al, 1998; de Vegt et al, 1998; Gimeno et al, 1998; Gomez-Perez et al, 1998; Ko et al, 1998; Wahl et al, 1998; Wiener et al, 1998; Shaw et al, 1999b).

Another consideration favouring the selection of the lower cutoff point for normality is the recent data relating FPG to mortality. Balkau et al (1999) showed that the relationship

between fasting glucose level and mortality followed a J-shaped curve except for fasting glucose and death from coronary heart disease which had a positive and linear relationship. While there was no clear threshold for fasting glucose, the lowest death rates were observed at a fasting blood glucose level of 5.5 mmol/l. Gerstein (1999) also concluded that if there is a dysglycaemic level above which individuals are at risk for cardiovascular disease it may be as low as 5.5 mmol/l for fasting values.

FPG is relatively stable changing by a mean of 0.06 mmol/l per decade of age whereas post challenge plasma glucose increases with age by a mean of 0.28 mmol/l (Blunt et al, 1991). The properties of FPG in detecting undiagnosed Type 2 diabetes may be influenced by age, in particular, the predictive values of FPG may decrease with increasing age. The data of Blunt et al (1991) support this. They compared two age groups, 50-64 and 65-79, and found that the sensitivity for an FPG above 5.5 mmol/l was nearly 100% for the younger age group and 75% for the older people while specificity was approximately 60% for both groups, and PPV was 12% and 25% respectively, reflecting the higher prevalence of diabetes in the older age group. However, this finding was not supported by two other studies. Bortheyry et al (1994) found similar sensitivities of 84-91% and specificities of 69-76% for each decade from 30-70 years using a fasting capillary blood glucose level of 5.6mmol/l as a cutoff for predicting the diagnosis of diabetes. Modan and Harris (1994) also reported similar sensitivities in their USA and Israeli populations for decades of age from 40-69 years. These differences may reflect the older age group included in the Blunt et al (1991) study but age does not seem to be a factor affecting the properties of FPG up to age 70.

The choice of cutoff value for FPG has implications for the number of people requiring definitive testing. The DECODE Study Group reported that by using a FPG above 5.5 mmol/l, 46% would require further testing compared with 12% using an FPG between 6.1-6.9 mmol/l (DECODE, 1999b). Similar results were reported from the Rancho Bernardo Study of US Caucasians aged 50-79 with diabetes prevalence of 10.6% (Blunt et al, 1991). With a FPG of 5.5 mmol/l or above, 41.4% would require further testing compared with 17.9% with a FPG of 6.1 mmol/l or above.

### **Summary – Fasting plasma glucose data**

- A number of studies suggest that a fasting plasma glucose of approximately 5.5 mmol/l defines the upper limit of normality
- Using a fasting plasma glucose cutoff value of 5.5 mmol/l and above for further testing for diabetes and IGT has acceptable sensitivity and specificity

### **2. *Random blood glucose***

Studies which have addressed the usefulness of random blood glucose (RBG) as a screening test for diabetes have mostly used random capillary blood glucose (RCBG) measured with a blood glucose meter. Therefore, 2 interrelated issues arise:

- The usefulness of random blood glucose/RCBG in case detection
- The accuracy of blood glucose meters in performing the testing

The attractiveness of this approach is obvious, especially in removing the need for fasting for opportunistic case finding in primary care. However, concern has been expressed about the inability to standardise the procedure.

#### **a] Usefulness of random blood glucose measurement in case detection**

There are few well designed studies which have properly addressed this question. The main methodological problem concerns the failure to determine the overall prevalence of

undiagnosed Type 2 diabetes in the cohort being studied by performing an OGTT on everyone.

Only two studies have examined the properties of RBG (measured by reflectance meter in both studies) as a screening tool for diabetes and performed an OGTT in the whole population irrespective of the RBG result. Qiao et al (1995) studied 1008 people and assessed RCBG measured with a reflectance meter compared with the OGTT result. Using a cutoff level for RCBG of 5.8 mmol/l achieved a sensitivity of 79% in men but only 40% in women while specificity was 86% and 84% respectively for men and women. The authors concluded that RCBG is too insensitive to use for routine screening for diabetes in a general population, particularly in populations with a known low prevalence of diabetes.

Engelgau et al (1995) performed a similar study in 828 people aged 20 and over and found that RCBG as a screening test for diabetes was significantly affected by age and the postprandial period. Compared with the OGTT, an RCBG of 5.6 mmol/l achieved a sensitivity ranging from 68-74% and specificity ranging from 66-77% depending on age. The authors concluded that it might be possible to use RCBG measurements for screening provided that age-specific cutoff values were also used.

Other studies have used various cutoff values for RCBG and have reached more favourable conclusions. However, these conclusions must be interpreted with caution due to the failure to assess the entire study population with an OGTT for undiagnosed diabetes, thereby limiting the interpretation of calculated sensitivity and specificity values. Andersson et al (1993) reported a sensitivity of 73% and specificity of 95% for a screening RCBG of 8 mmol/l or more for diagnosing diabetes on the basis of two fasting blood glucose values of  $\geq 6.7$  mmol/l. Bitzen and Schersten (1986) collected venous blood samples (measured in the laboratory and also by reflectance meter) in 1082 people visiting a primary health care centre in Sweden. People with an RBG of  $\geq 7$  mmol/l underwent an OGTT. Meter measured random venous blood glucose gave a sensitivity of 75% and specificity of 98%. Murphy et al (1993), in a field study in Alaska, reported on an RCBG measured with either a meter or visual blood glucose strip. People with a random blood glucose of  $\geq 6.7$  mmol/l had an OGTT. Compared with a laboratory measured FPG, the meter gave a sensitivity of 75% and specificity 93% and the visual strip 71% and 94% respectively. Simmons and Williams (1994), in the Coventry Diabetes Study, tested approximately 7000 people with an RCBG measured in a laboratory followed up with an OGTT if the result was  $\geq 6$  mmol/l within 2 hour of eating or  $\geq 5$  mmol/l if 2 hours or more has elapsed since eating (as well as 10% of people with results below these levels). At an RCBG of  $7 \geq$  mmol/l the sensitivity was 52% in Europeans and the specificity was 94%. They concluded that screening asymptomatic individuals using an isolated RCBG was a poor test for detecting diabetes.

There is another potential difficulty with RBG measurement. Even the studies in which the entire population was tested with an OGTT, the results have been interpreted according to the 1985 WHO criteria (in which the fasting plasma threshold was 7.8 mmol/l). The performance of a RBG measurement is likely to be slightly worse with the new lower fasting plasma glucose criteria since people who have diabetes diagnosed only on the new, lower fasting value (and have a non-diabetic 2-hour value) are more likely to have a normal random blood glucose value.

#### b) The use of blood glucose meters in performing the testing

The ADA (1993) stipulates that blood glucose meters should give a reading within 10% of the reference value. Although the clinical relevance of this has been questioned, it is an appropriate objective in the context of screening of an individual for possible undiagnosed diabetes. There have been numerous studies examining the accuracy of blood glucose meters (not reviewed here). However, few blood glucose meters are capable of achieving this level of accuracy, even under ideal circumstances. For example, Poirier et al (1998) found that 5 modern meters using non-wipe technology were only able to achieve this level of accuracy 36-68% of the time. The general conclusion is that commercially available blood glucose meters perform well in the context of self monitoring but are not sufficiently accurate for screening or diagnosis.

Many of the studies cited previously on the usefulness of RBG testing used meter measured RCBG (Bitzen and Schersten, 1986; Andersson et al, 1993; Engulgau et al, 1995; Qiao et al, 1995). The overall results of these studies confirm that this method of screening for diabetes is not sufficiently sensitive or is subject to variations which make standardisation difficult (eg effect of time since last meal, gender differences).

In addition to their use for testing for undiagnosed diabetes in health care environments, blood glucose meters have also been used for diabetes screening in the general community. Newman et al (1994) recently examined community screening in public places using various meters and various operators. The yield of undiagnosed diabetes was considerably lower than expected from prevalence studies. The overall conclusion was that it is difficult to justify glucose-based community screening in low risk populations because of the inherent inaccuracy of the method, dangers associated with handling of potentially infectious, blood contaminated supplies, and potential medical and legal ramifications of blood testing. Furthermore, the authors concluded that the data supported the ADA white paper of abandoning glucose-based community screening.

Despite the findings of this literature review that screening for undiagnosed diabetes with RBG testing is inferior to fasting plasma glucose testing, measurement of a fasting sample may be considered impractical under certain circumstances eg inconvenient or a high chance that the individual will not comply with returning for a fasting plasma glucose measurement. Under such circumstances, measurement of random blood glucose may be performed. However, there are two further qualifications:

- The measurement should be performed in the laboratory and not by using a blood glucose meter
- Follow up testing is required for a result within the range of 5.5 to 11.0 mmol/l.

The study of Welborn et al (1997) provides support for further testing if the RBG level is  $\geq 5.5$  mmol/l. Using cutoff values below this resulted in substantially less people with undiagnosed diabetes being detected – 15% fewer with a cutoff of  $\geq 6.0$  mmol/l, 29% less with a cutoff of  $\geq 6.5$  mmol/l and 41% less with a cutoff of  $\geq 7.0$  mmol/l.

#### **Summary – Random blood glucose data**

- Random blood glucose measurements are not as discriminatory as fasting plasma glucose in detecting undiagnosed Type 2 diabetes
- Blood glucose meters are not sufficiently accurate for screening an individual for possible undiagnosed Type 2 diabetes
- Random blood glucose measurements using a blood glucose meter is not recommended
- Glucose-based community screening is not recommended

- If random blood glucose is used for screening, the measurement should be performed in a laboratory (not using a blood glucose meter) and follow up testing is required for a result between 5.5 and 11.0 mmol/L.

### 3. *Urine glucose*

Urine glucose as a screening test for undiagnosed Type 2 diabetes proposed in the 1990 contracts with British general practitioners (Mant & Fowler, 1990). It is another potentially simple method and was and was advocated by the British Diabetic Association for population screening (Paterson, 1993). The usefulness of this technique has been addressed in a few recent studies. However, only one study included performing an OGTT in the entire study population to determine the true prevalence of undiagnosed Type 2 diabetes (Davies et al, 1993).

Davies et al (1993) assessed 442 people from the Isle of Ely, UK with a urine test and an OGTT. Participants were asked to perform a self-test for postprandial glycosuria using urine strips the day prior to having the OGTT. The sensitivity of a positive urine test was 43% and specificity 98%.

Other studies have reported on the properties of urine testing but have not tested the whole population with an OGTT. Friderichsen and Maunsbach (1997) screened 2242 people with a self-test for postprandial glycosuria and tested all people with a positive result and a random sample of 106 negative screenees with an OGTT. The study showed a sensitivity of 20.8% and specificity of 99.1%. Andersson et al (1993) reported a sensitivity of 23% and specificity of 99% for a positive urinalysis for diagnosing diabetes on the basis of two fasting blood glucose values of  $\geq 6.7$  mmol/l. Bitzen and Schersten (1986) reported sensitivities of 30-59% and specificities of 97-99% for random urine samples for a variety of methods of urine testing. Each of these authors concluded that the sensitivity of urine glucose testing was too low and was therefore a suboptimal method for early case detection of Type 2 diabetes. However, Davies et al (1999a) reached a different conclusion arguing that despite low response rates to their mailed out self-test program (34.4% in Asian Indians and 54% in Caucasians) and the low yield of undiagnosed diabetes compared with population estimates, that this method compares well with other methods and is an economical way to perform community screening.

Hanson et al (1993) studied 237 Pima Indians with non-fasting urine glucose and non-fasting OGTT and reported a sensitivity of 64.3% and specificity of 98.8% for a positive urine test for diabetes diagnosed on the 2-hour non-fasting post glucose load plasma glucose result. This higher sensitivity may reflect the study methodology or population differences including the younger age of the participants (mean age 30) and age related differences in renal thresholds.

#### **Summary - Urine glucose data**

- The sensitivity of urine glucose testing is too low for screening individuals for undiagnosed Type 2 diabetes
- Urine glucose testing is not recommended for screening individuals for undiagnosed Type 2 diabetes

### 4. *Glycated haemoglobin*

Glycated haemoglobin (HbA<sub>1c</sub>) has been suggested and evaluated as a potential test for screening and diagnosing Type 2 diabetes in keeping with a desire to have a simple and single test which could replace the OGTT. HbA<sub>1c</sub> is attractive since it requires no preparation of the subject and directly relates to treatment targets. Although a number of studies have

addressed this issue, this review focuses on studies which have measured HbA<sub>1c</sub>, rather than studies in which HbA<sub>1</sub> was measured.

Peters et al (1996) performed a systematic review of articles published between 1966 and 1994 in which glycated haemoglobin was measured concurrently with performing an OGTT. Authors of identified studies were contacted to provide individual data for all subjects and ultimately data were available on 11 276 individuals and the final analysis was performed on the data from 8 984 people in whom HbA<sub>1c</sub> was measured. When an HbA<sub>1c</sub> plus 4SDs was used as a cutoff point, the sensitivity was 36% and specificity was 100% compared with an OGTT. An HbA<sub>1c</sub> cutoff point of 6.1% identified 41% of non-diabetic subjects and 21% with IGT. The authors modelled different HbA<sub>1c</sub> levels and concluded that HbA<sub>1c</sub> measurement may represent a reasonable approach to identifying treatment-requiring diabetes.

A more recent study by Wiener and Roberts (1998) studied 401 non-pregnant adults and found that one third of people with diabetes diagnosed by an OGTT had values of HbA<sub>1c</sub> within the normal range (up to 5.5%), but that all people with HbA<sub>1c</sub> of  $\geq 6.2\%$  had diabetes (i.e. specificity was 100%), but the sensitivity was only 41%. They concluded that HbA<sub>1c</sub> does not fulfill the criteria for a test to substitute for the OGTT because of its low sensitivity.

Davidson et al (1995) reviewed the findings of 16 articles in which glycated haemoglobin was measured and participants also had an OGTT. Ninety five per cent of people with a glycated haemoglobin value of 1% or more above the upper limit of normal had diabetes based on the WHO 1985 criteria (WHO, 1985). Based on this review the authors conclude that an FPG should be used to screen for diabetes followed by an HbA<sub>1c</sub> to diagnose diabetes in those with an indeterminate FPG result. They suggested that detection of lesser degrees of diabetes in people with indeterminate FPG detected by OGTT makes no difference to management since people with this 'milder' form of diabetes would be treated with diet and exercise because they already have HbA<sub>1c</sub> results in the treatment target range, namely within 1% of the upper limit of normal. Davidson et al (1999) pursued this theme in examining HbA<sub>1c</sub> measurement in the cohorts from the NHANES III study (Harris et al, 1998) and from the Meta-Analysis Research Group (Peters et al, 1996). With the new ADA criteria for diagnosing diabetes (ADA, 1997), 60% of people in both datasets having diabetes diagnosed on the basis of an FPG of 7.0-7.7 mmol/l had normal HbA<sub>1c</sub> and one third had results within 1% of the upper limit of normal. Using the previous criteria of an FPG of  $\geq 7.8$  mmol/l to diagnose diabetes, 50-60% had elevated HbA<sub>1c</sub>. Although this proposition has some attraction, the authors concede that it is yet to be tested. Furthermore, while the proposal is predicated on the role of glycation as an established and important process in the development of microvascular complications, the contribution of glycation to macrovascular complications is uncertain and there is accumulating evidence that mortality is closely linked with post glucose load hyperglycaemia, a situation which would not be detected in the majority of people using HbA<sub>1c</sub> measurement (Barrett-Connor and Ferrara, 1998; DECODE, 1998; Shaw et al, 1999c).

The results of this review support the WHO (1999) and ADA (1997) position that HbA<sub>1c</sub> is not recommended for diagnosis of diabetes. As well as its low sensitivity in detecting undiagnosed diabetes, measurement of HbA<sub>1c</sub> is not yet standardised around the world and therefore it is not currently possible to produce diagnostic thresholds that would be valid in all laboratories. Furthermore, Kilpatrick et al (1998) assessed the biological variation of HbA<sub>1c</sub> in non-diabetic subjects and on the basis of a significant interindividual variance (85% of total test variance) concluded measuring of HbA<sub>1c</sub> has inherent limitations which limit its usefulness as a screening test for diabetes.

Whether HbA<sub>1c</sub> measurement might prove useful in the future as a confirmatory test for the diagnosis of suspected diabetes requires further study. Current regulations in Australia on the clinical use of HbA<sub>1c</sub> measurement which attract a Medicare benefit preclude its use for this purpose.

#### **Summary - Glycated haemoglobin data**

- The sensitivity of HbA<sub>1c</sub> measurement is too low to use as a method for identifying people with undiagnosed Type 2 diabetes
- HbA<sub>1c</sub> measurement is not recommended as a test for identifying people with undiagnosed Type 2 diabetes

#### **5. Fructosamine**

Although used less frequently than HbA<sub>1c</sub> measurement, fructosamine is another method used to monitor diabetes control. Fructosamine measures serum glycosylated protein concentration and its properties have also been studied as a potential single test option for screening and diagnosing diabetes.

Croxson et al (1991) measured fructosamine in 264 non-diabetic individuals aged 65-85 years who also had a modified OGTT (75g oral glucose load and measurement of plasma glucose after 2-hour). Using a fructosamine cutoff of 1.92 mmol/l, the sensitivity for detecting diabetes diagnosed on the 2-hour post glucose load plasma glucose was 74% and specificity was 95%. Similar results were reported in an elderly population by Cefalu et al (1993). They studied 147 non-diabetic people aged 65-88 years. Using a fructosamine cutoff point of 260 umol/l, the sensitivity for diagnosis of undiagnosed diabetes compared with an OGTT was 69% and specificity was 95%. Salemans et al (1987) studied 183 individuals and reported that with a fructosamine cutoff point (corrected for albumin) of 2.50 mmol/l sensitivity for undiagnosed diabetes was 67% and specificity was 96%.

The results of other studies have not been as good. Guillausseau et al (1990) compared fructosamine and OGTT in 144 subjects and showed that the sensitivity of an abnormal fructosamine result was only 19% with a specificity of 97%. In another study of 738 people selected for further testing on the basis of a positive urinary glucose, Sekikawa et al (1990) reported a sensitivity for a fructosamine cutoff value of 2.9 mmol/l of 23% and specificity of 98%. The study of Shima et al (1989) of 302 adults showed that elevated fructosamine values gave a sensitivity of 53% and specificity of 97% for diabetes diagnosed by OGTT. Swai et al (1988) studied 613 people in Tanzania and found that a fructosamine of above the mean plus 2 SDs had a sensitivity of 22% and specificity of 99% compared with the OGTT. Finally, Yamanouchi et al (1991) tested 1034 people. A fructosamine value of 3.0 mmol/l had a sensitivity of 59% and specificity of 97% compared with OGTT diagnosed diabetes.

These studies demonstrate a wide range of sensitivities of fructosamine for detecting undiagnosed Type 2 diabetes and do not define a cutoff which could be applied in routine practice. Goldstein (1998) concluded that it is difficult to draw any overall conclusions from fructosamine data.

#### **Summary – Fructosamine data**

- Studies on fructosamine as a test for undiagnosed Type 2 diabetes have given a wide range of sensitivities (19% to 74%)
- Fructosamine is not recommended as a test for undiagnosed Type 2 diabetes

#### **6. Comparability of measurements of blood glucose**

Accurate and precise measurement of glucose concentration in the circulation is essential in the diagnosis and management of diabetes. However, what is often assumed to be straightforward is not always the case, as discussed in the review by Burrin and Alberti (1990). Glucose oxidase is the standard laboratory method used to measure glucose in the circulation. The most important variables in interpreting a result for glucose in the circulation are the origin of the sample (ie arterial, capillary or venous), and whether the glucose is measured in plasma or whole blood. The analysis of each sample incorporates a combination of these 2 variables with the most common combinations being venous plasma, venous whole blood and capillary whole blood. Most laboratories measure venous plasma glucose (occasionally venous whole blood) while meters measure capillary whole blood glucose.

The ADA has only published values for venous plasma glucose to assess glucose status (ADA, 1997) while the WHO provide equivalence estimates of diagnostic values for venous plasma, venous whole blood, capillary plasma, and capillary whole blood (WHO, 1999) (Appendix 1).

In general venous samples give slightly lower values than capillary samples. These differences may be generally ignored in the fasting state but after a meal or glucose load capillary samples are stated to be about 8% higher than venous samples and at a normal haematocrit, venous samples are 14-16% higher than whole blood (Burrin & Alberti, 1990). The different diagnostic levels in the WHO tables attempt to incorporate these empirical differences (WHO, 1999). However, the few studies which have systematically compared results in different blood samples raise doubts about the published equivalence values for the purposes of diagnosing diabetes in an individual, as opposed to their use for determining the population prevalence of diabetes.

Neely et al (1991) examined the influence of sample type on the interpretation of the OGTT. Considering only the non-pregnant group, the mean plasma-whole blood difference at the glucose level to diagnose IGT was 0.67 mmol/l and at the level to diagnose diabetes was 1.0 mmol/l. The authors concluded that mathematical conversion from whole blood to plasma is inexact and dependent on ambient glucose levels. Also individual variations in non-fasting capillary-venous differences were found to be too great to allow for meaningful translation from venous to capillary values. The capillary-venous differences were observed to be in steep decline during the second hour of the OGTT and the differences are likely to be smaller than the 1.1mmol/l suggested by WHO (WHO, 1999).

Farrer et al (1995) compared venous capillary and venous whole blood measurements during OGTT testing at 3 and 12 months in a prospective study of 353 people who had undergone coronary artery bypass graft surgery. Similar plasma-whole blood glucose differences were found as in the Neely et al study (1991) – at a glucose level of 5.5 mmol/l the mean difference at 3 and 12 months was 0.45 mmol/l, 0.82 mmol/l at a level of 7.8 mmol/l and 1.23 mmol/l at a level of 11.1 mmol/l. There was no significant difference in the proportion of people classified at 12 months with diabetes or IGT using either the venous whole blood glucose or venous plasma glucose interpreted using the WHO 1985 criteria (5% v 4.6% for diabetes and 21.1% v 17.6% for IGT). Although these differences were not significant in terms of population prevalence of diabetes and IGT, they encompass differences which would translate into individuals being classified differently depending on blood sample choice.

Studies also suggest an anomaly in the published WHO equivalence values below which diabetes is unlikely (WHO, 1999), whereby a venous plasma glucose value of 5.5 mmol/l is equated to a venous whole blood glucose or a capillary whole blood glucose level of 4.4

mmol/l – a 1.1 mmol/l difference. The study of Neely et al (1991) and Farrer et al (1995) both indicate that this difference is in the order of 0.5 mmol/l rather than 1.1 mmol/l. This is supported by Simmons and Williams (1994) who reported the fasting venous plasma glucose to be 0.56 mmol/l higher than the capillary whole blood level. These studies indicate that the equivalence of a venous plasma glucose of 5.5 mmol/l should be a capillary whole blood glucose in the order of 5 mmol/l.

### **Summary - Comparability of measurements of blood glucose data**

- Sample type and method of analysis influence the result of blood glucose measurement
- These differences are not necessarily corrected by empirical calculations
- These differences do not seem to affect population prevalence studies
- These discrepancies are of sufficient magnitude to influence the diagnosis of diabetes or IGT in an individual
- Venous plasma glucose measurements should be used whenever possible to test for undiagnosed Type 2 diabetes
- A fasting capillary whole blood glucose of 5.0 mmol/l is equivalent to a fasting venous plasma glucose of 5.5 mmol/l

### **The WHO 1999 criteria should be used to diagnose diabetes**

#### ***1. The oral glucose tolerance test***

A key difference between the recommendations of the WHO (WHO, 1999) and the ADA (ADA, 1997) on the diagnosis of diabetes is the place of the OGTT. The ADA does not recommend the OGTT for routine clinical use for several reasons – the lower FPG of 7.0 mmol/l equates well with the 2-hour post glucose load plasma glucose level of 11.1 mmol/l; the OGTT is not widely used because of perceived inconvenience to patients and physicians views that it is unnecessary, costly and time consuming; and the repeat test reproducibility is not as good as the FPG. On the other hand the WHO continues to recommend the OGTT in people with blood glucose values in the uncertain range. The Australian Diabetes Society expressed reservations about discontinuing the use of the OGTT and suggested its continued use pending the final decision of the WHO (Colman et al, 1999). The following examines the evidence on the different positions of the WHO and ADA about the OGTT.

#### **a] The equivalence of fasting plasma glucose and 2-hour plasma glucose levels**

The ADA publication cites the data used to support an FPG of 7 mmol/l being associated with the same risk of microvascular disease as a 2-hour level of 11.1 mmol/l (ADA, 1997). However the data with respect to macrovascular disease available at that time was not as convincing.

Table 15 summarises studies which have compared population prevalence rates determined by the 1997 ADA criteria (ADA, 1997) compared with the 1985 WHO (WHO, 1985) criteria. These studies show a wide range of results in prevalence rates using these different criteria. However, a consistent finding was that even when prevalence rates were similar, the 2 criteria did not recognise the same group of individuals as having diabetes. The overall concordance rates for diabetes using the 2 criteria was of the order of 65%. Differences in concordance rates may be modulated by increasing age, which is associated with an increase in 2-hour plasma glucose levels, gender (Pomerlau, 1999), and weight (DECODE, 1999b; Shaw et al, 1999a), with people with a lower BMI having lower FPG levels and consequently less diabetes diagnosed on the basis of a FPG measurement.

It should be noted that in the 1985 WHO criteria an abnormal FPG was defined as 7.8 mmol/l or more. Using the 1999 WHO criteria (WHO, 1999) all people diagnosed by the

ADA criteria will be classified as having diabetes, since the new FPG level for diagnosing diabetes is now 7.0 mmol/l or more for both ADA and WHO. However, only 75% of people identified by the 1999 WHO criteria will have diabetes by the ADA criteria (Shaw et al, 1999a) but much lower overlap (41%) has been reported (Vaccaro et al, 1999).

One reason for the discrepancy between the 1999 WHO and 1997 ADA criteria is that the equivalence of an FPG of 7.0 mmol/l and a 2-hour level of 11.1 mmol/l has not been confirmed in all populations. For example, the DECODE Study Group (DECODE, 1999c) reported that in a wide range of European populations, the FPG which predicts a 2-hour value of 11.1 mmol/l was 6.4 mmol/l in men and 5.8 mmol/l in women. Cockram et al (1992) and Chang et al (1998) reported similar findings in Chinese populations with the FPG equivalent to a 2-hour plasma glucose of 11.1 mmol/l being 5.7 mmol/l and 6.0 mmol/l respectively. Burke et al (1998) reported that it would be necessary to lower the FPG to 6.4 mmol/l to equate to 11.1 mmol/l in the San Antonio Heart Study which included both Mexican Americans and non-Hispanic whites. Koehler et al (1999) reported the corresponding level to be 6.8 mmol/l from their RIAD study data. This contrasts with the data from the Pacific Islands (Finch et al, 1990a) and India (Ramachandran et al, 1993) which are consistent with the data in the ADA publication (ADA, 1997).

The studies cited in Table 15 also demonstrate a discrepancy between the IFG and IGT categories which are not equivalent in identifying the same group of individuals. The significance of this is unknown. While there are considerable data on the significance of IGT (Alberti, 1996), there are relatively little data on IFG. While more data are required to answer this question, 2 recent studies provide some information. The DECODE study (DECODE, 1999a) found a small increase in mortality associated with IFG in men but not women compared to a greater and significant increase in both men and women with IGT. Barzilay et al (1999) examined data from the Cardiovascular Health Study in adults 65 years and older and found similar relative risks for coronary artery disease, stroke and cardiovascular death in people with IFG and IGT. However, the number of cases attributable to IFG was less than with IGT since there were twice as many people with IGT than with IFG.

Are there any consequences of having an elevated 2-hour plasma glucose and a normal FPG, a condition which has been termed isolated post challenge hyperglycaemia (IPH)? IPH can only be identified using an OGTT. Its prevalence is variable but approximates 25% of people with a diagnosis of diabetes based on an OGTT interpreted according to WHO criteria. As discussed above, the prevalence of IPH increases with age and is more common in women and among the non-obese. Data from 3 studies suggests that IPH is not a benign condition. The Rancho Bernardo study examined risk of fatal cardiovascular disease in people aged 50-89 years and found a multiply adjusted hazards ratio for fatal cardiovascular disease of 2.6 and for heart disease of 2.9 in women but not men with IPH (Barrett-Connor & Ferrara, 1998). The DECODE study used data from 13 European prospective cohort studies which included 18 048 men and 7 316 women aged 30 years or older. IPH was associated with a hazards ratio for death of 1.21 (CI 1.04-1.40) for men but a non-significant increase in women. Shaw et al (1999c) studied the effect of IPH in populations from Mauritius, Fiji and Nauru. Hazards ratios were significantly increased for all-cause mortality in both men (2.7) and women (2.0) and for cardiovascular mortality (men 2.3, women 2.6). Interestingly, this study also showed a significant association of IPH with cancer death in men (hazard ratio 8.0).

**Table 15: Comparison of prevalence of diabetes diagnosed by ADA 1997 and WHO 1985 criteria**

| Reference         | Based on FPG $\geq 7$ mmol/l [ADA 1997]              | Based on 2-h PG $\geq 11.1$ mmol/l [WHO, 1985] |
|-------------------|--|--|
| Costa, 1999       | 1.8%   | 3.2%   |
| Davies, 1999      | 44.8%  | 33.1%  |
| DECODE 1999b      | 7.7%   | 7.2%   |
| DECODE 1998 #     | -4.0 to +13.2%                                       |  |
| de Vegt, 1998     | 5%   | 5%   |
| Gimeno, 1998      | 19.2%  | 20.3%  |
| Gomez-Perez, 1998 | 4.6%   | 13%  |
| Harris, 1997      | 4.4%   | 6.4%   |
| Ko, 1998          | 13.7%  | 21.8%  |
| Kousta, 1999      | 11.5%  | 13.3%  |
| Mannucci, 1999a   | 11.4%  | 20.1%  |
| Mannucci, 1999b   | 18.2%  | 25.5%  |
| Okubo, 1999       | 3.5%   | 8.2%   |
| Pomerleau, 1999   | 5.6% - total<br>6.4% - men<br>3.3% - women           | 4.6% - total<br>4.7% - men<br>4.2% - women     |
| Ramachandran 1998 | 4.3%   | 5.2%   |
| Rathmann, 1999    | 6.5%   | 4.6%   |
| Shaw, 1999b #     | +4.1% to -2.8%                                       |  |
| Unwin, 1998       | Europeans 7.8%<br>Chinese 6.2%<br>South Indian 21.4% | 4.8%<br>4.7%<br>20.1%                          |
| Vaccaro, 1999     | 3.2%   |  |
| Wahl 1998         | 7.7%   | 14.8%  |

# Included a number of studies. Results are range of difference compared with WHO, 1985 criteria

b) Reproducibility of the oral glucose tolerance test

One of the reasons for the ADA recommending against the routine use of the OGTT was concern about its lack of reproducibility.

This issue was examined in the Hoorn study (Mooy et al, 1996). Repeat testing with an OGTT was performed over a 2 to 6 week period and the diagnostic categories compared in 555 people without known diabetes. The reproducibility of normal glucose tolerance was 91%, 48% for IGT and 78% for diabetes. Most of the movement was in the IGT category in which prevalence decreased from 11.5% on the first test to 5.6% on the second test with most people moving from IGT to normal. Only one person moved from the diabetic to normal category and that occurred between the first and second tests.

Ko et al (1998) examined the reproducibility of the OGTT in 212 Chinese people 6 weeks apart. The overall reproducibility was 65.6% with the reproducibility of normal glucose tolerance being 95%, IGT 44% and diabetes 59%. Again, most of the change related to movement in the IGT category. However, 4 subjects changed to normal from diabetes between the first and second test.

An earlier study by Ericksson and Lingarde (1990) administered a 30g/m<sup>2</sup> OGTT on 2 occasions within one month to 889 men whose initial fasting blood glucose was above 6.5 mmol/l. Test reproducibility was 88% for normal glucose tolerance, 31% for IGT and 45% for diabetes. Thirteen men moved from diabetes to normal and 7 from normal to diabetes between the first and second tests.

Reversion from diabetic to non-diabetic status is a recognised phenomenon. In the San Antonio Heart Study the reversion rate from diabetes, diagnosed either by the WHO 1980 criteria (which required both an elevated FPG  $\geq 7.8$  and an elevated 2-hour plasma glucose of  $\geq 11.1$  mmol/l) or the ADA 1997 criteria, to normal glucose tolerance was approximately 12% over an 8 year period. The reason for this phenomenon is unknown but is more likely to occur with lower baseline plasma glucose levels and may be related to lifestyle changes (Burke et al, 1998).

Most studies which have looked at OGTT reproducibility have noted that fewer individuals have an abnormality of glucose tolerance on the second test. Mooy et al (1996) suggest that this might be related to stress because heart rate was lower on the second test. Another possibility is self imposed lifestyle changes between tests. However biological variation is a significant contributor. Cummings and Fraser (1988) studied 14 healthy people aged 23-48 years who each had 10 OGTTs repeated at approximately 1 week intervals. The coefficient of variation of the tests was 11%, but no individual moved from normal into either the IGT or diabetes category.

Care should be taken to perform the OGTT under standardised conditions and to assure the quality of the procedure. Factors which can interfere with the test (eg smoking) must be avoided.

Studies to date have all assessed OGTT reproducibility using the WHO 1985 criteria and the effect, if any, of the new diagnostic criteria of the lower FPG value combined with the 2-hour value, has not been studied. It may be that the more reproducible FPG will improve the performance of the OGTT. Also no studies have specifically examined the reproducibility of the OGTT in the diagnostically uncertain range of FPG between 5.5 and 6.9 mmol/l.

### **Summary - Oral glucose tolerance test data**

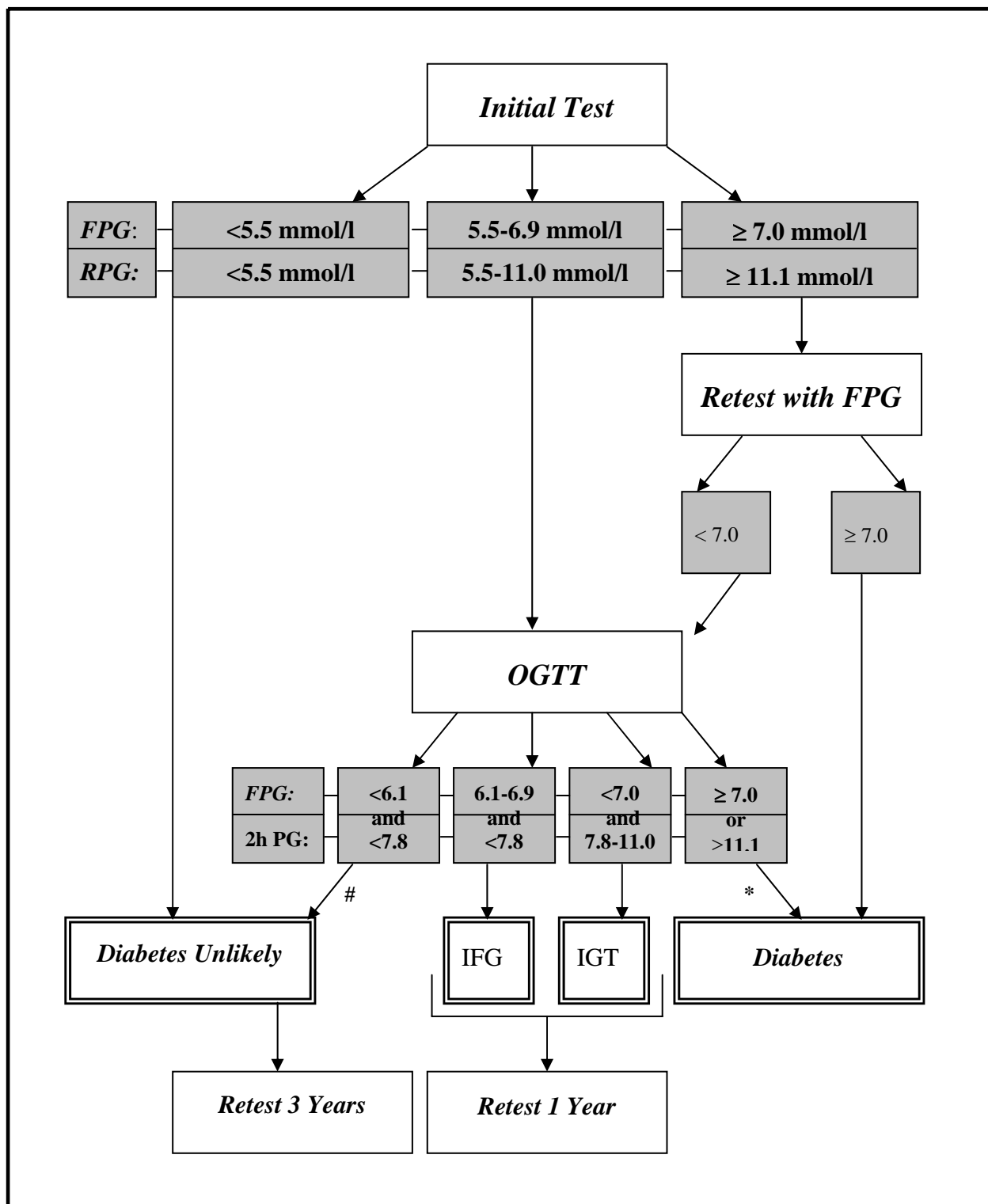
- Use of a fasting plasma glucose of 7.0 mmol/l and above alone to diagnose diabetes identifies a different subgroup of people to that identified by the 2-hour post glucose plasma glucose level of 11.1 mmol/l with overall concordance approximating 65%
- The fasting plasma glucose level which corresponds to the 2-hour post glucose plasma glucose level of 11.1 mmol/l has been variously reported to be between 5.7 and 7.0 mmol/l
- Isolated elevation of the 2-hour post glucose load plasma glucose level is associated with increased mortality
- The overall reproducibility of the OGTT is approximately 65%
- Most of the problems with OGTT reproducibility relate to people with IGT and few people with normal glucose tolerance are misclassified as having diabetes
- The WHO recommendation to test people in the uncertain range of blood glucose readings with an OGTT is supported

### **2. *The diagnosis of diabetes must be confirmed by retesting***

The diagnosis of diabetes has important consequences for the individual beyond health implications eg insurance. Several studies cited in this review illustrate the biological variation in plasma glucose measurement. Although this is most obvious with the OGTT, fasting plasma glucose is also subject to intra-individual variation. It is therefore essential that the diagnosis of diabetes in an asymptomatic individual is confirmed by testing on separate days.

Although this may be considered cumbersome, time consuming and inconvenient it is imperative that an individual is not labeled with a diagnosis of diabetes without confirming the diagnosis. The following flow chart outlines the procedure for making a diagnosis of diabetes in an asymptomatic non-pregnant individual.

**Flow Chart: Testing for and Diagnosing Type 2 Diabetes**



FPG – fasting plasma glucose

RPG – random plasma glucose

OGTT – oral glucose tolerance test

IFG – impaired fasting glucose

IGT – impaired glucose tolerance

\* diagnosis must be confirmed by further testing if initial FPG 5.5-6.9mmol/l or RPG 5.5-11.0mmol/L.

# people with an initial plasma glucose consistent with a diagnosis of diabetes or IGT/IFG which is not confirmed on subsequent testing should be retested after 1 year and subsequent testing interval determined according to the 1 year result

## Comments – How to Detect Type 2 Diabetes

The fasting plasma glucose provides a simple and reliable method of screening for undiagnosed Type 2 diabetes. Additionally, the majority of all those with undiagnosed Type 2 diabetes will have a diagnostic fasting plasma glucose (FPG  $\geq 7.0$  mmol/l), and will not need an OGTT (although they will need a confirmatory fasting test). A fasting plasma glucose has superior sensitivity than a random glucose measurement. However, in the context of opportunistic screening, situations may arise when it is not feasible to perform a fasting test where a random sample may be used.

Despite the practical attraction of restricting diabetes diagnosis (and its exclusion in high risk people) to the fasting plasma glucose, there is evidence that a substantial proportion of those with undiagnosed diabetes have a non-diabetic fasting value and can only be diagnosed by the 2-hour value. People whose only abnormality is an elevated 2-hour glucose have increased mortality and are at risk of the usual diabetes related complications. Therefore the OGTT is necessary to exclude diabetes in an individual with an elevated plasma glucose in the diagnostically uncertain range.

Available data support the WHO position that the cutoff value of fasting plasma glucose for excluding people from further testing should be less than 5.5 mmol/l.

Blood glucose meters have been used in screening programs for diabetes. However, the properties of a random blood glucose measured by a blood glucose meter, coupled with the relative imprecision of blood glucose meters, make this an unsuitable method for routine use in testing for undiagnosed diabetes. The definitive diagnosis of diabetes must always be made on laboratory measurements.

Available data do not support the use of urine testing or glycated haemoglobin or fructosamine measurement to detect people with undiagnosed Type 2 diabetes.

The implications for an individual of a diagnosis of diabetes should not be underestimated and therefore the diagnosis should be secure and the number of false positive results limited. Given the day to day variability of blood glucose measurements, diabetes should only be diagnosed when two abnormal values have been found on separate days. However, it should be noted that all the studies relating risk of retinopathy to blood glucose levels on which the diagnostic thresholds for diabetes have been derived, have only used a single OGTT.

It should also be noted that the evidence on which diagnostic thresholds are based is for venous plasma glucose. The thresholds given for other sample types (eg whole blood) represent calculated empirical equivalence values and formal comparisons in large populations have not been made. This raises uncertainty in using these calculated values in the diagnosis of diabetes in individuals.

Plasma glucose measurement may be affected by acute intercurrent illness (eg myocardial infarction see Section 2 - Cardiovascular Disease). These situations may introduce additional uncertainties in making a diagnosis of diabetes. Minor elevations of plasma glucose should be interpreted with caution and testing should be repeated after recovery from the acute episode.

These guidelines make no distinction between screening people in the different high risk groups for undiagnosed Type 2 diabetes, including women with previous gestational diabetes (GDM). These recommendations differ from the consensus statement of the Australasian Diabetes in Pregnancy Society (Hoffman, 1998) which recommends periodic post partum testing with an OGTT. Kousta et al (1999) noted a discordance between the 1997 ADA criteria and the 1985 WHO criteria in women with previous GDM similar to that observed in other populations (Table 15). However, there are no data to suggest that previous GDM requires surveillance procedures different to the rest of the high risk community.

## Evidence Table: Fasting Plasma Glucose

| Author  | Evidence          |                 |                |                     |                  |
|---|-------------------|-----------------|----------------|---------------------|------------------|
|   | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|   | Level             | Study Type      |                |                     |                  |
| <b>Appleton CA (1999)</b><br>(Adults – Australia)               | III <sup>#</sup>  | Cross-sectional | Medium         | High <sup>-</sup>   | High             |
| <b>Balkau B (1999)</b><br>(Adults – France)                     | II <sup>#</sup>   | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Blunt BA (1991)</b><br>(Adults – US)                         | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Bortheiry AL (1994)</b><br>(Adults – Brazil)                 | III <sup>#</sup>  | Cross-sectional | Medium         | High <sup>+</sup>   | Low              |
| <b>Chang C (1998)</b><br>(Adults – Taiwan)                      | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | Medium           |
| <b>Cockram CS (1992)</b><br>(Adults & Adolescence – China)      | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | Medium           |
| <b>Costa A (1999)</b><br>(Adults – Spain)                       | III <sup>#</sup>  | Cross-sectional | Medium         | High <sup>-</sup>   | High             |
| <b>Davies MJ (1993)</b><br>(Adults – UK)                        | III <sup>#</sup>  | Cross-sectional | Medium         | Medium <sup>-</sup> | High             |
| <b>de Vegt F (1998)</b><br>(Adults – The Netherlands)           | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>DECODE Study (1999b)</b><br>(Adults – Europe)                | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | High             |
| <b>Diamond TH (1999)</b><br>(Adults – Australia)                | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | High             |
| <b>Gimeno SGA (1998)</b><br>(Adults – Brazil)                   | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | Low              |
| <b>Gomez-Perez FJ (1998)</b><br>(Adults – Mexico)               | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | Low              |
| <b>Harris MI (1997)</b><br>(Adults – US)                        | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | High             |
| <b>Ko GTC (1998)</b><br>(Adults – Hong Kong)                    | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | Medium           |
| <b>Larsson H (1995)</b><br>(Adults women – Sweden)              | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | High             |
| <b>Modan M (1994)</b><br>(Adults – US; Israel)                  | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | High             |
| <b>Ramachandran A (1993)</b><br>(Adults – India)                | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | Medium           |
| <b>Shaw JE (1999b)</b><br>(Adults – Pacific Islands; Mauritius) | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | Medium           |
| <b>Wahl PW (1998)</b><br>(Adults – US)                          | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | High             |
| <b>Wiener K (1995)</b><br>(Adults & Adolescence – UK)           | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Wiener K (1998)</b><br>(Adults & Adolescence – UK)           | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>+</sup> | High             |

<sup>#</sup> Studies assessed using the non-intervention assessment system

<sup>+</sup> Fasting plasma glucose is effective at diagnosing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Evidence Table: Random Blood Glucose and Blood Glucose Meters

| Author  | Evidence          |                 |                |                     |                  |
|---|-------------------|-----------------|----------------|---------------------|------------------|
|   | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|   | Level             | Study Type      |                |                     |                  |
| <b>Andersson DKG (1993)</b><br>(Adults – Sweden)              | III <sup>#</sup>  | Cohort          | Medium         | High <sup>+</sup>   | High             |
| <b>Bitzen PO (1986)</b><br>(Adults – Sweden)                  | III <sup>#</sup>  | Cross-sectional | Medium         | Medium <sup>+</sup> | High             |
| <b>Engelgau MM (1995)</b><br>(Adults - Egypt)                 | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | Low              |
| <b>Murphy NJ (1993)</b><br>(Adults – US: Alaskan Indian)      | III <sup>#</sup>  | Cross-sectional | Medium         | Medium <sup>+</sup> | Low              |
| <b>Newman WP (1994)</b><br>(Adults – US)                      | III <sup>#</sup>  | Cross-sectional | Medium         | Medium <sup>-</sup> | High             |
| <b>Poirier J (1998)</b><br>(Adults - France)                  | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Qiao Q (1995)</b><br>(Adults - Finland)                    | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>+</sup> | High             |
| <b>Simmons D (1994)</b><br>(Adults – UK: European, Sth Asian) | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | High             |
| <b>Welborn TA (1997)</b><br>(Adults – Australia)              | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |

<sup>#</sup> Studies assessed using the non-intervention assessment

<sup>+</sup> Blood glucose meters are effective at diagnosing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Evidence Table: Urine Glucose

| Author  | Evidence                 |                   |                       |                         |                         |
|---|--------------------------|-------------------|-----------------------|-------------------------|-------------------------|
|   | <i>Level of Evidence</i> |                   | <i>Quality Rating</i> | <i>Magnitude Rating</i> | <i>Relevance Rating</i> |
|   | <i>Level</i>             | <i>Study Type</i> |                       |                         |                         |
| <b>Andersson DKG (1993)</b><br>(Adults - Sweden)                | III <sup>#</sup>         | Cohort            | Medium                | High <sup>+</sup>       | High                    |
| <b>Bitzen PO (1986)</b><br>(Adults - Sweden)                    | III <sup>#</sup>         | Cross-sectional   | Medium                | Medium <sup>+</sup>     | High                    |
| <b>Davies MJ (1993)</b><br>(Adults - UK)                        | III <sup>#</sup>         | Cross-sectional   | Medium                | High <sup>+</sup>       | High                    |
| <b>Davies MJ (1999)</b><br>(Adults - UK: Cuacasian, Indo-Asian) | III <sup>#</sup>         | Cross-sectional   | Medium                | Medium <sup>+</sup>     | High                    |
| <b>Friderichsen B (1997)</b><br>(Adults - Denmark)              | III <sup>#</sup>         | Cross-sectional   | Medium                | Low                     | High                    |
| <b>Hanson RL (1993)</b><br>(Adults - US: Pima Indian)           | III <sup>#</sup>         | Cross-sectional   | High                  | Medium <sup>+</sup>     | Low                     |

<sup>#</sup> Studies assessed using the non-intervention assessment

<sup>+</sup> Urine glucose is effective at diagnosing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by '+' for a positive effect and '-' for a negative effect. Low = no statistically significant effect

## Evidence Table: Glycated Haemoglobin

| Author   | Evidence          |                 |                |                     |                  |
|--|-------------------|-----------------|----------------|---------------------|------------------|
|  | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|  | Level             | Study Type      |                |                     |                  |
| <b>Barrett-Connor E (1998)</b><br>(Elderly – US)               | II <sup>#</sup>   | Cohort          | High           | High <sup>-</sup>   | High             |
| <b>Davidson MB (1999)</b><br>(Adults – US)                     | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>+</sup> | High             |
| <b>DECODE Study (1998)</b><br>(Adults – Europe)                | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | High             |
| <b>Kilpatrick ES (1998)</b><br>(Adults – US)                   | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>-</sup> | High             |
| <b>Peters AL (1996)</b>  | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Shaw JE (1999c)</b><br>(Adults- Mauritius; Pacific Islands) | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup>   | Medium           |
| <b>Wiener K (1998)</b><br>(Adults – UK)                        | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |

<sup>#</sup> Studies assessed using the non-intervention assesment

<sup>+</sup> Glycated haemoglobin is effective at diagnosing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Evidence Table: Fructosamine

| Author   | Evidence          |                 |                |                     |                  |
|--|-------------------|-----------------|----------------|---------------------|------------------|
|  | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|  | Level             | Study Type      |                |                     |                  |
| <b>Cefalu WT (1993)</b><br>(Elderly - US)                      | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Croxson SCM (1991)</b><br>(Elderly - UK)                    | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>+</sup> | High             |
| <b>Guillausseau PJ (1990)</b><br>(Adults- France)              | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>-</sup> | High             |
| <b>Salemans THB (1987)</b><br>(Adult women: - The Netherlands) | III <sup>#</sup>  | Case-control    | High           | Medium <sup>+</sup> | High             |
| <b>Sekikawa A (1990)</b><br>(Adults - Japan)                   | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>-</sup> | Low              |
| <b>Shima K (1989)</b><br>(Adults - Japan)                      | III <sup>#</sup>  | Cross-sectional | Medium         | Medium <sup>-</sup> | Low              |
| <b>Swai ABM (1988)</b><br>(Adults - Tanzania)                  | III <sup>#</sup>  | Cross-sectional | High           | Low                 | Low              |
| <b>Yamanouchi T (1991)</b><br>(Adults - Japan)                 | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>-</sup> | Low              |

<sup>#</sup> Studies assessed using the non-intervention assessment

<sup>+</sup> Fructosamine is effective at diagnosing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by '+' for a positive effect and '-' for a negative effect.

Low = no statistically significant effect

## Evidence Table: Comparison of Measurement of Blood Glucose

| Author  | Evidence          |                 |                |                   |                  |
|---|-------------------|-----------------|----------------|-------------------|------------------|
|   | Level of Evidence |                 | Quality Rating | Magnitude Rating  | Relevance Rating |
|   | Level             | Study Type      |                |                   |                  |
| Farrer M (1995)<br>(Adults - UK)                        | III <sup>#</sup>  | Cohort          | High           | High <sup>+</sup> | High             |
| Neely RDG (1991)<br>(Adult women - UK)                  | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup> | High             |
| Simmons D (1994)<br>(Adults – UK: Europids,<br>Indians) | III <sup>#</sup>  | Cross-sectional | High           | High <sup>-</sup> | High             |

<sup>#</sup> Studies assessed using the non-intervention assessment

<sup>+</sup> A comparison of blood glucose is effective at diagnosing Type 2 diabetes.

**Magnitude rating:** The direction of the effect is by '+' for a positive effect and '-' for a negative effect.

## Evidence Table: The Oral Glucose Tolerance Test

| Author  | Evidence          |                 |                |                     |                  |
|---|-------------------|-----------------|----------------|---------------------|------------------|
|   | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|   | Level             | Study Type      |                |                     |                  |
| <b>Barrett-Connor E (1998)</b><br>(Elderly – US)                                    | II <sup>#</sup>   | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Barzilay JI (1999)</b><br>(Elderly – US)   | II <sup>#</sup>   | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Burke JP (1998)</b><br>(Adults – US: Mexican & non-Hispanic whites)              | III <sup>#</sup>  | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Chang C (1998)</b><br>(Adults – Taiwan)  | III <sup>#</sup>  | Cross-sectional | Medium         | High <sup>+</sup>   | Medium           |
| <b>Cockram CS (1992)</b><br>(Adults & Adolescence – China)                          | III <sup>#</sup>  | Cross-sectional | Medium         | High <sup>+</sup>   | Medium           |
| <b>Costa A (1999)</b><br>(Adult men – Spain)  | III <sup>#</sup>  | Cross-sectional | Medium         | High <sup>+</sup>   | High             |
| <b>Cummings ST (1988)</b><br>(Adults – Scotland)                                    | III <sup>#</sup>  | Cross-sectional | Medium         | High <sup>+</sup>   | High             |
| <b>Davies MJ (1999)</b><br>(Adults - UK)  | III <sup>#</sup>  | Cross-sectional | Medium         | Medium <sup>+</sup> | High             |
| <b>De Vegt F (1998)</b><br>(Adults – The Netherlands)                               | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>DECODE Study (1998)</b><br>(Adults – Europe)                                     | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>+</sup> | High             |
| <b>DECODE Study (1999a)</b><br>(Adults – Europe)                                    | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>DECODE Study (1999b)</b><br>(Adults – Europe)                                    | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Eriksson KF (1990)</b><br>(Adults – Sweden)                                      | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Finch CF (1990a)</b><br>(Adults – Pacific Islands)                               | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | Medium           |
| <b>Gimeno SGA (1998)</b><br>(Adults – Brazil: Japanese)                             | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | Low              |
| <b>Gomez-Perez FJ (1998)</b><br>(Adults – Mexico)                                   | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | Low              |
| <b>Harris MI (1997)</b><br>(Adults – US)  | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Ko GTC (1998)</b><br>(Adults – Hong Kong)  | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | Medium           |
| <b>Koehler C (1999)</b><br>(Adults- Germany)  | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Kousta E (1999)</b><br>(Women – UK)  | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>+</sup> | High             |
| <b>Mannucci E (1999a)</b><br>(Adults – Italy)                                       | III <sup>#</sup>  | Cross-sectional | Medium         | High <sup>+</sup>   | High             |
| <b>Mannucci E (1999b)</b><br>(Adults – Italy)                                       | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Mooy JM (1996)</b><br>(Adults – The Netherlands)                                 | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Okubo M (1997)</b><br>(Adults – US: Japanese)                                    | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | Low              |
| <b>Pomerleau J (1999)</b><br>(Adults – UK: Europeans, South Asians, Afro-Caribbean) | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Ramachandran A (1998)</b><br>(Adults- India)                                     | III <sup>#</sup>  | Cross-sectional | High           | Medium <sup>+</sup> | Medium           |
| <b>Rathmann W (1999)</b><br>(Adults – Germany)                                      | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Shaw JE (1999b)</b><br>(Adults – Mauritius; Pacific Is)                          | III <sup>#</sup>  | Cohort          | High           | Medium <sup>+</sup> | Medium           |
| <b>Unwin N (1998)</b><br>(Adults – UK: Chinese, Sth Asian, European)                | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |
| <b>Vaccaro O (1999)</b><br>(Adults – Italy)   | II <sup>#</sup>   | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Wahl PW (1998)</b><br>(Adults- US)   | III <sup>#</sup>  | Cross-sectional | High           | High <sup>+</sup>   | High             |

<sup>#</sup> Studies assessed using the non-intervention assessment. <sup>+</sup> An oral glucose tolerance test is effective at diagnosing Type 2 diabetes.  
**Magnitude rating:** The direction of the effect is by '+' for a positive effect and '-' for a negative effect

# Section 4 : Case Detection and Diagnosis

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## Issue

**How often should testing be performed?**

## Recommendations

Periodic testing for undiagnosed Type 2 diabetes is recommended by measuring fasting plasma glucose according to the following schedule:

- Each year for people with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
- Every 3 years for people at high risk\* with a negative screening blood test
- People with an initial plasma glucose consistent with a diagnosis of diabetes or IGT/IFG which is not confirmed on subsequent testing should be retested after 1 year

All people with identified risk factors for Type 2 diabetes who have a negative screening test are at risk of cardiovascular disease and the future development of Type 2 diabetes, and should be given appropriate advice on risk factor reduction

\* High risk status is defined on p139

## Evidence statements

- The annual rate of progression to diabetes from IGT and IFG is high and warrants annual testing for undiagnosed Type 2 diabetes  
*Evidence Level III-2*
- The annual incidence of diabetes among people with other risk factors for diabetes is 1-2% and warrants screening every 3 years  
*Evidence Level III-2*
- There is a low risk of the development of retinopathy over a 4-5 year period following a negative screening test for diabetes  
*Evidence Level III-2*

## Background – How Often to Test

Most people identified as being at risk through risk factor assessments, remain at increased risk for the future development of Type 2 diabetes. The majority of risk factors used to identify at risk people are not modifiable. The natural history of IGT includes individuals who may revert to normal glucose tolerance (Alberti, 1996). Since IFG is a new category of glucose intolerance, its natural history has not yet been well documented. Obesity as a risk factor can be modified by weight loss. Blood glucose testing only excludes diabetes at a particular point in time. Therefore, those people who have risk factors but have a negative initial screening or diagnostic blood test require ongoing surveillance and testing for the future development of Type 2 diabetes.

There has been virtually no published research about the optimal interval for retesting at risk people following a negative screening test for diabetes. The literature search identified only one paper which partly addressed this question (Davies & Day, 1994).

The overall objective of this guideline is to identify risk factors associated with a 5% prevalence of undiagnosed Type 2 diabetes in order to recommend further testing in these groups of people. The purpose of this section is to determine a time period during which at risk people who were tested and in whom the result was negative, will have progressed to a point where they again have a significant chance of having undiagnosed Type 2 diabetes. Whereas for the initial test the guideline identified risk factors associated with a 5% prevalence of undiagnosed diabetes, for the retesting interval this review attempted to identify a time period during which the incidence of diabetes reaches 5%.

An additional consideration is the risk that an individual in whom diabetes has been excluded by testing, could have progressed to diabetes and developed diabetes related complications before the next testing time point.

## Evidence – How Often to Test

### Progression to diabetes

#### *1. Impaired glucose tolerance/impaired fasting glucose*

The annual incidence of development of Type 2 diabetes in people with IGT and IFG has been reviewed in Section 2 of this guideline.

The average annual rate of progression in Caucasians is 4.7%, 7.7% in Aboriginal and Torres Strait Islander populations and 6.2% in Pacific Island people. In these studies on IGT, these rates compare with average annual incidence rates for Type 2 diabetes of 0.7% in Caucasian people with normal glucose tolerance but is dependent on age, being less in younger people (see Table 1, Section 2).

Only a small number of studies have reported on the annual conversion rate from IFG to Type 2 diabetes. In Caucasian populations, Charles et al (1991) reported an annual progression rate of 1% and Vaccaro et al (1999) reported rates of 2.2% while rates of 5.8% were reported from Mauritius (Shaw et al, 1999a).

From these data, it can be concluded that the rate of progression of IGT to diabetes warrants annual testing for undiagnosed diabetes. The situation with IFG is still unclear because it is a relatively new category and there have been insufficient studies which have addressed this question. Given the range of progression reported in the 3 studies, it is suggested that

individuals with IFG should also be tested annually, at least until there is more information about the natural history of IFG.

## 2. *Women with previous gestational diabetes mellitus (GDM)*

The mean annual incidence of diabetes in predominantly Caucasian women with previous GDM is 1.4%, 14 times greater than in the control group (0.1%) (see Table 2, Section 2). From these data it would take 3-4 years for the overall incidence rates to reach 5%. Therefore, it is recommended that women with previous GDM should be retested every 3 years for undiagnosed Type 2 diabetes.

This recommendation differs from that of the Australasian Diabetes in Pregnancy Society (ADIPS) which advocates second yearly testing of women with previous GDM. However, the ADIPS position was formulated using a consensus approach and the rationale for choosing a 2 year interval was not stated, apart from acknowledging the increased risk of future development of Type 2 diabetes in these women (stated as 50% over a 20 year period) (Hoffman et al, 1998).

The guideline conclusion to retest women with previous GDM every 3 years represents minimum criteria. More frequent retesting may be appropriate depending on clinical circumstances, especially during the child bearing years.

In addition to periodic testing for undiagnosed Type 2 diabetes, it is recommended that all women with a pregnancy complicated by GDM should be tested 6-8 weeks postpartum for the presence of permanent diabetes (Hoffman et al, 1998). However, it should be noted that this issue was outside the scope of this guideline and the evidence for this recommendation has not been reviewed as part of the development of this guideline.

## 3. *Others risk factors*

A number of studies have reported on the annual incidence of progression from normal glucose tolerance to Type 2 diabetes. The results of studies which used an OGTT to identify normality at baseline and to follow up participants in populations relevant to Australia are summarised in Table 16.

**Table 16: Annual rates of progression from normal glucose tolerance to Type 2 diabetes**

| Population                     | Age of population studied | Annual progression to Type 2 diabetes | Reference      |
|--------------------------------|---------------------------|---------------------------------------|----------------|
| <b>Caucasians</b>              |                           |                                       |                |
| France                         | 50-60                     | 0.9%                                  | Charles, 1991  |
| Finland                        | 65-84                     | 0.8%                                  | Stengard, 1993 |
| Finland                        | 65-74                     | 0.9%                                  | Mykkanen 1993  |
| Malta                          | 35-69                     | 0.7%                                  | Schranz, 1989  |
| USA – San Antonio Heart Study* | 25-64                     | 0.6%                                  | Haffner, 1997  |
| Mauritius                      | 25-74                     | 0.9%                                  | Shaw, 1999     |
| Nauru                          | ≥ 20                      | 1.2%                                  | Dowse, 1991    |
| Taiwan, Kinman Islands         | > 30                      | 1.8%                                  | Chou, 1998     |

\* Non-Hispanic Whites

The annual rate of progression in Caucasian populations ranged from 0.6-0.9%, with the higher rates observed in the older age groups. This is evident from the Haffner et al (1997) study in which the annual incidence of Type 2 diabetes was 0.4% in people aged 25 to 44 years and 1% in people aged 45-65 years.

Only limited data are available in other populations (Table 16). Shaw et al (1999a) reported 0.9% annual incidence of developing diabetes in Mauritius, but their study population covered a wide age range. The data from Nauru demonstrate that annual incidence of progression is 1.5 to 2-fold higher in people aged 35-54 years compared with younger ages (Dowse et al, 1991).

The results of other studies in Caucasian populations which used a variety of methods to diagnose diabetes, have reported generally similar findings to those contained in Table 16 (Ohlson et al, 1988; McPhillips et al, 1990; Skarfors et al, 1991; Lipton et al, 1993; Shaten et al, 1993; Perry et al, 1995; Vilbergsson et al, 1997; Njolstad et al, 1998).

In some studies progression rates for high risk individuals within the study population have been reported. Obesity increases the annual incidence of progression by approximately 2-fold (Lipton et al, 1993; Perry et al, 1995; Haffner et al, 1997; Njolstad et al, 1998;). A family history of diabetes or the presence of hypertension also influence the rate of progression. Ohlson et al (1988), Skarfors et al (1991), Mykkanen et al (1993) and Shaten et al (1993) and each showed a 1.5 to 2-fold increase in the rate of progression in people with a positive family history for diabetes. Hypertension shows a similar increase (Mykkanen et al, 1993; Skarfors et al, 1991).

There are no specific data on the other risk factors for the future development of Type 2 diabetes identified in Section 2 of this Guideline.

Overall, these data suggest that risk factors are associated with a 1.5 to 2-fold increase in the annual rate of progression from normal glucose tolerance to Type 2 diabetes. Since the average annual incidence of progression in Caucasian populations is 0.8% (Table 16), the influence of risk factors would increase this to 1.2-1.6% each year and it would therefore takes between 3-4 years to reach a 5% incidence of diabetes.

### **The Development of Diabetes Complications**

The other consideration in determining an appropriate retesting interval is the likelihood of development of diabetes complications between successive testing. Provided people present for testing, case detection programs will detect most of the people with severer degrees of hyperglycaemia who are at particular risk of the development of complications. In the US NHANES III study (Harris et al, 1998) 30% of all people with undiagnosed Type 2 diabetes were in this category. The mean HbA<sub>1c</sub> of this group was 8.2%, levels which are associated with the development of microvascular complications.

Few prospective studies have addressed the development of diabetes complications in people as their glucose tolerance declines from normal (or slightly impaired) to overt diabetes. In a small study of British men with IGT (Jarrett, 1986), retinopathy took a minimum of five years to develop after the onset of diabetes. Diabetes was determined by annual OGTT, and retinopathy was detected by clinical ophthalmoscopy. In a larger study of Pima Indians (Nagi et al, 1997), the prevalence of retinopathy in people who were newly diagnosed by screening and had had a non-diabetic OGTT (which could have been IGT) within the previous 4 years was 8.3%. Unpublished data from Mauritius (Zimmet, 1999c) show that of 79 people screened as having undiagnosed diabetes by OGTT who had a normal glucose tolerance test five years earlier, 8.9% had retinopathy at the time of diabetes diagnosis. In both of the last two studies, retinopathy was diagnosed by retinal photography and there were no instances of vision threatening retinopathy.

These limited data indicate that there is some risk of the development of non-vision threatening retinopathy in the interval between a negative test and a subsequent positive test for diabetes, and that this risk is of the order of 8% over a 4 to 5 year period.

### **Other Data**

Davies and Day (1994) performed the only study which directly examined a specific screening interval. They used subject self testing of postprandial urine at an interval of 30 months. The authors concluded that this type of screening program was worthwhile in terms of response rate (1<sup>st</sup> screen -79%, 2<sup>nd</sup> screen -73%) and yield of new cases of diabetes (1<sup>st</sup> screen - 0.72%, 2<sup>nd</sup> second screen - 0.44% [NS]).

### **Comments – How Often to Test**

A variety of consensus recommendations regarding retesting intervals for undiagnosed diabetes have been made. The ADA and BDA recommend a screening interval of 3 years in high risk people with a negative screening test (Paterson, 1993; ADA, 2000). The New Zealand Society for the Study of Diabetes (NZSSD, 1995) recommends screening intervals between 1-5 years, depending on risk category. The WHO does not make a specific recommendation (WHO, 1999).

The incidence data reviewed here confirm that IGT (and IFG) are associated with the highest risk of progression to Type 2 diabetes and that individuals with a current diagnosis in either of these categories should be retested every year.

For the other high risk groups for which data are available, intervals of 3-4 years are associated with a 5% incidence of progression to new diabetes. Taking into consideration these data, the risk of development of retinopathy over a 4-5 year period, and the desire to have a simple and practical guideline, a retesting interval of 3 years is recommended for all other risk categories.

The exclusion of diabetes in people who are at risk should not be seen as an “all clear”. These people, irrespective of their current blood glucose level, are at risk of cardiovascular disease and future diabetes. Apart from informing these individuals about the need for future retesting, they should be informed about their risk status, the possibility of development of diabetes in the future, and the symptoms of diabetes. They should also receive advice on diet and physical activity in an attempt to modify their risk.

## Evidence Table: How Often Should Testing be Performed?

| Author  | Evidence          |                 |                |                     |                  |
|---|-------------------|-----------------|----------------|---------------------|------------------|
|   | Level of Evidence |                 | Quality Rating | Magnitude Rating    | Relevance Rating |
|   | Level             | Study Type      |                |                     |                  |
| <b>Charles MA (1991)</b><br>(Adult men - France)                                  | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Chou P (1998)</b><br>(Adults - Kinmen Islands;Taiwan)                          | III-2             | Cohort          | High           | High <sup>+</sup>   | Medium           |
| <b>Davies M (1994)</b><br>(Adults-UK)   | III-2             | Cohort          | Medium         | Medium <sup>+</sup> | High             |
| <b>Dowse GK (1991)</b><br>(Adults- Nauru)   | III-2             | Cross-sectional | High           | High <sup>-</sup>   | Medium           |
| <b>Haffner SM (1997)</b><br>(Adults- US: Mexican Americans & non-Hispanic whites) | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Jarrett JR (1986)</b><br>(Adult men - UK)                                      | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Lipton RB (1993)</b><br>(Adults - US: African American and whites)             | III-2             | Cohort          | Medium         | High <sup>+</sup>   | High             |
| <b>McPhillips JB (1990)</b><br>(Adults – US)                                      | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Mykkanen L (1993)</b><br>(Elderly – Finland)                                   | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Nagi DK (1997)</b><br>(Adults - US: Pima Indians)                              | III-2             | Cohort          | High           | High <sup>+</sup>   | Low              |
| <b>Njolstad I (1998)</b><br>(Adults – Norway)                                     | III-2             | Cohort          | Medium         | High <sup>+</sup>   | High             |
| <b>Ohlson L-O (1988)</b><br>(Adult men - Sweden)                                  | III-2             | Cohort          | Medium         | High <sup>+</sup>   | High             |
| <b>Perry IJ (1995)</b><br>(Adult men - UK)  | III-2             | Cohort          | Medium         | High <sup>+</sup>   | High             |
| <b>Schranz AG (1989)</b><br>(Adults – Malta)                                      | III-2             | Cohort          | High           | Medium <sup>+</sup> | High             |
| <b>Shaten BJ (1993)</b><br>(Adult men -US)  | III-2             | Cohort          | Medium         | High <sup>+</sup>   | High             |
| <b>Shaw JE (1999a)</b><br>(Adults – Mauritius)                                    | III-2             | Cohort          | High           | High <sup>+</sup>   | Low              |
| <b>Skarfors ET (1991)</b><br>(Adult men- Sweden)                                  | III-2             | Cohort          | High           | High <sup>+</sup>   | High             |
| <b>Stengard JH (1993)</b><br>(Elderly men - Finland)                              | III-2             | Cohort          | High           | Medium <sup>+</sup> | High             |
| <b>Vaccaro O (1999)</b><br>(Adults – Italy)                                       | III-2             | Cohort          | Medium         | High <sup>+</sup>   | High             |
| <b>Vilbergsson S (1997)</b><br>(Adults- Iceland)                                  | III-2             | Cohort          | Medium         | High <sup>+</sup>   | Low              |
| <b>Zimmet (1999c)</b><br>(Adults – Mauritius)                                     | III-2             | Cross-sectional | High           | High <sup>+</sup>   | Low              |

<sup>+</sup> Testing to diagnose Type 2 diabetes should be performed regularly.

**Magnitude rating:** The direction of the effect is by ‘+’ for a positive effect and ‘-’ for a negative effect.

## Appendix 1

### Values for diagnosis\* of diabetes and other categories of hyperglycaemia

|                                    | Glucose concentration, mmol/l |                     |                     |                     |
|------------------------------------|-------------------------------|---------------------|---------------------|---------------------|
|                                    | Plasma                        |                     | Whole blood         |                     |
|                                    | Venous                        | Capillary           | Venous              | Capillary           |
| <b>Diabetes Mellitus:</b>          |                               |                     |                     |                     |
| Fasting                            | ≥ 7.0                         | ≥ 7.0               | ≥ 6.1               | ≥ 6.1               |
| <i>or</i>                          |                               |                     |                     |                     |
| 2-h post glucose load              | ≥ 11.1                        | ≥ 12.2              | ≥ 10.0              | ≥ 11.1              |
| <b>Impaired Glucose Tolerance:</b> |                               |                     |                     |                     |
| Fasting concentration              | < 7.0                         | < 7.0               | < 6.1               | < 6.1               |
| <i>and</i>                         |                               |                     |                     |                     |
| 2-h post glucose load              | ≥ 7.8 and<br>< 11.1           | ≥ 8.9 and<br>< 12.2 | ≥ 6.7 and<br>< 10.0 | ≥ 7.8 and<br>< 11.1 |
| <b>Impaired Fasting Glucose:</b>   |                               |                     |                     |                     |
| Fasting                            | ≥ 6.1 and<br>< 7.0            | ≥ 6.1 and<br>< 7.0  | ≥ 5.6 and<br>< 6.1  | ≥ 5.6 and<br>< 6.1  |
| 2-h (if measured)                  | < 7.8                         | < 8.9               | < 6.7               | < 7.8               |

\*Note that diabetes can only be diagnosed in an individual when these diagnostic values are confirmed on another day.

## Case Detection and Diagnosis: Evidence References

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## 2.5 Case Detection & Diagnosis Guideline Search Strategy And Yield

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### Electronic databases searched:

Medline

Embase

CINAHL

Cochrane

Evidence-Based Medicine Reviews (EBM)

### Terms used to search the databases:

Detailed within the table to follow.

### Search inclusion criteria:

Where possible the searches were limited by the English language and human research.

Year of publication: Medline 1985-99, Embase 1988-99, Cinahl 1985-1999 Cochrane: all years:

Year ranges other than those detailed above are specified next to each set of key words in the table.

### Other searching:

Reference lists at the end of articles of particular relevance were hand searched.

Relevant articles were solicited from expert colleagues and organisations.

Local and international clinical practice guidelines were reviewed for relevant references

### Abbreviations and explanation of table headings

The term NIDDM was used to signify Diabetes Mellitus/ non-insulin dependent

The database searched has been indicated next to each key word or set of key words using the following abbreviations

M = Medline; EM = Embase; CI = Cinahl; CO =Cochrane; .mp = free text search term; / = MESH term; LDL = Low density lipoprotein; HDL = High density lipoprotein;

VLDL = very low density lipoprotein; ep = epidemiology, pa = pathology, pc = prevention & control, di = diagnosis, et = etiology, cl = classification, co = complications,

**Identified** = number of articles which matched the mesh terms listed or contained the text terms in each particular database

**Relevant** = those articles considered relevant to the questions being asked after viewing titles or abstracts

**Articles identified by other strategies** = articles identified by hand searching, other searches for other questions, or from colleagues

**Total for Review** = Those articles which were relevant to the question, contained original data or were systematic reviews of original articles and met the following criteria.

### *Criteria used to determine the suitability of articles for review*

In assessing the evidence the following criteria were used to determine the suitability of studies:

1. Method for diagnosis of Type 2 diabetes

The hierarchy for considering articles was:

- Oral glucose tolerance test (OGTT) with collection of fasting and 2 hour post glucose load blood samples interpreted using WHO criteria (either 1985 or 1999)
- OGTT with collection of only the 2 hour post glucose load blood sample interpreted using WHO criteria
- OGTT interpreted using National Diabetes Data Group criteria
- Fasting plasma glucose – 1997 ADA or 1999 WHO criteria
- Fasting plasma glucose – 1985 WHO criteria
- Non fasting blood glucose
- Medical records with explicit criteria for confirming diagnosis
- Self reported diabetes (unconfirmed)

These different methods for diagnosing diabetes were aggregated for the purpose of defining the “Quality Level” for the overall evidence rating for each study as follows: High = use of OGTT; Medium = other non OGTT related blood sample; Low = no blood test i.e. reported diabetes only.

Since not all questions or issues raised in formulating the guideline have literature with OGTT diagnosed diabetes, in some areas it was necessary to include studies with less stringent diabetes diagnostic criteria.

2. Selection of subjects - unbiased and representative of the general population being studied

3. Studies containing data on newly diagnosed diabetes separate from people with known diabetes

4. Studies dealing with risk factors for diabetes were considered if they:

- included data predominantly relating to Caucasians, Aboriginal and Torres Strait Islanders, or Other populations with high prevalence of Type 2 diabetes represented in Australia
- were prospective or cross sectional studies which considered newly diagnosed Type 2 diabetes
- cross sectional studies on people with established Type 2 diabetes were not be used
- reported standardised data
- included multivariate analyses when more than 1 risk factor was reported

| QUESTIONS  |  | KEY WORDS  | NO. ARTICLES IDENTIFIED | NO RELEVANT ARTICLES | ARTICLES IDENTIFIED BY OTHER STRATEGIES | TOTAL FOR REVIEW | LEVEL I  | LEVEL II  | LEVEL III | LEVEL IV | TOTAL NO REVIEWED & GRADED | HIGHEST LEVEL OF EVIDENCE |  |
|--|--|--|-------------------------|----------------------|---|------------------|----------|-----------|-----------|----------|----------------------------|---------------------------|--|
| <b>1.</b>  | <b>Is case detection and diagnosis for Type 2 diabetes worthwhile?</b> | <b>Total For Question</b>                              | <b>650</b>              | <b>114</b>           |   | <b>81</b>        | <b>1</b> | <b>24</b> | <b>6</b>  | <b>0</b> | <b>31</b>                  | <b>I</b>                  |  |
|  |  | Mass screening/ AND (NIDDM/di, OR diabetes mellitus) M | 74                      | 1                    |   |                  |          |           |           |          |                            |                           |  |
|  |  | NIDDM/ep AND mass screening/ M                         | 69                      | 17                   |   |                  |          |           |           |          |                            |                           |  |
|  |  | NIDDM/ep AND mass screening/ M (91-95)                 | 107                     | 17                   |   |                  |          |           |           |          |                            |                           |  |
|  |  | NIDDM/ep AND Case finding.mp M(91-95)                  | 4                       | 2                    |   |                  |          |           |           |          |                            |                           |  |
|  |  | NIDDM/pc.ep AND screening.mp M                         | 77                      | 5                    |   |                  |          |           |           |          |                            |                           |  |
|  |  | NIDDM/ AND screening.mp M                              | 14                      | 5                    |   |                  |          |           |           |          |                            |                           |  |
|  |  | NIDDM/ep AND Screening.mp EM                           | 69                      | 17                   |   |                  |          |           |           |          |                            |                           |  |
|  |  | Prediabetic state/ AND Mass screening/ M (all yrs)     | 17                      | 2                    |   |                  |          |           |           |          |                            |                           |  |
|  |  | Health screening/ AND NIDDM/ep/di CI                   | 18                      | 3                    |   |                  |          |           |           |          |                            |                           |  |
|  |  | Diabetes AND screening CO                              | 124                     | 5                    |   |                  |          |           |           |          |                            |                           |  |
| Mass screening/ AND diabetes mellitus/ AND false positive reaction M | 10   | 5  |                         |                      |   |                  |          |           |           |          |                            |                           |  |
| Prediabetic state/ ep, cl, co AND NIDDM M                            | 67   | 2  |                         |                      |   |                  |          |           |           |          |                            |                           |  |

| QUESTIONS  |  | KEY WORDS  | NO. ARTICLES IDENTIFIED | NO RELEVANT ARTICLES | ARTICLES IDENTIFIED BY OTHER STRATEGIES | TOTAL FOR REVIEW | LEVEL I  | LEVEL II   | LEVEL III | LEVEL IV | TOTAL NO REVIEWED & GRADED | HIGHEST LEVEL OF EVIDENCE |
|--|--|--|-------------------------|----------------------|---|------------------|----------|------------|-----------|----------|----------------------------|---------------------------|
| 2.   | <b>Who should be tested for undiagnosed Type 2 diabetes?</b> | <b>Total For Question</b>  | <b>4715</b>             | <b>490</b>           | <b>4</b>                                | <b>203</b>       | <b>3</b> | <b>131</b> | <b>67</b> | <b>0</b> | <b>203</b>                 | <b>I</b>                  |
|  | <b>GENERAL RISK FACTORS</b>                                  | NIDDM/ep, AND risk assessment/ M   | 7                       | 2                    |   |                  |          |            |           |          |                            |                           |
|  |  | NIDDM/ep AND (risk of diabetes/ OR Risk factor/ EM                                     | 249                     | 32                   |   |                  |          |            |           |          |                            |                           |
|  |  | NIDDM/ AND (Risk factors/ OR Risk assessment/) CO                                      | 95                      | 2                    |   |                  |          |            |           |          |                            |                           |
|  |  | Prediabetic state/ AND risk factors/ M (all yrs)                                       | 53                      | 5                    |   |                  |          |            |           |          |                            |                           |
|  |  | Risk factors/ OR risk of diabetes.mp AND NIDDM/ep,di CI                                | 47                      | 3                    |   |                  |          |            |           |          |                            |                           |
|  |  | Diabetes mellitus /pc, ep, di AND pregnancy/ or gestational diabetes EM                | 76                      | 12                   |   |                  |          |            |           |          |                            |                           |
|  |  | Risk factor AND diabetes mellitus/pc, ep, di AND pregnancy OR gestational diabetes/ EM | 12                      | 3                    |   |                  |          |            |           |          |                            |                           |
|  | <b>SPECIFIC RISK FACTORS</b>                                 | NIDDM/ AND risk factors AND gestational/ M (all yr)                                    | 69                      | 6                    |   |                  |          |            |           |          |                            |                           |
|  |  | Diabetes mellitus/ ep AND blood glucose/ and gestational.mp M (all yrs)                | 9                       | 4                    |   |                  |          |            |           |          |                            |                           |
| Diabetes/ AND risk factors/ AND gestational.mp OR birthweight/ & .mp OR fetal macrosomia/ CI |  | 12   | 2                       |                      |   |                  |          |            |           |          |                            |                           |
|  |  | NIDDM/pc,ep,di AND gestational diabetes/ M (all  | 38                      | 2                    |   |                  |          |            |           |          |                            |                           |

| QUESTIONS |  | KEY WORDS   | NO. ARTICLES IDENTIFIED | NO RELEVANT ARTICLES | ARTICLES IDENTIFIED BY OTHER STRATEGIES | TOTAL FOR REVIEW | LEVEL I | LEVEL II | LEVEL III | LEVEL IV | TOTAL NO REVIEWED & GRADED | HIGHEST LEVEL OF EVIDENCE |  |
|-----------|--|---|-------------------------|----------------------|---|------------------|---------|----------|-----------|----------|----------------------------|---------------------------|--|
| <b>2.</b> | <b>Who should be tested for undiagnosed Type 2 diabetes?</b> | Cardiovascular/ AND diabetes mellitus/ AND glucose/ AND (prospective/ OR follow/) AND Diabetes mellitus, non-insulin dependent/ M | <b>133</b>              | <b>8</b>             |   |                  |         |          |           |          |                            |                           |  |
|           |  | NIDDM/ep, di AND cardiovascular disease/ M  | <b>77</b>               | <b>6</b>             |   |                  |         |          |           |          |                            |                           |  |
|           |  | Cardiovascular disease/ AND undiagnosed diabetes.mp M(96-99)  | <b>5</b>                | <b>2</b>             |   |                  |         |          |           |          |                            |                           |  |
|           |  | Cardiovascular disease AND glucose intolerance/ (91-99)M  | <b>54</b>               | <b>19</b>            |   |                  |         |          |           |          |                            |                           |  |
|           |  | Blood glucose/ AND cardiovascular disease/ (91-99) M  | <b>222</b>              | <b>15</b>            |   |                  |         |          |           |          |                            |                           |  |
|           |  | NIDDM/ep, di AND Myocardial infarction/ M   | <b>13</b>               | <b>2</b>             |   |                  |         |          |           |          |                            |                           |  |
|           |  | NIDDM/ AND (CVD/ OR CVA/ OR myocardial infarction/ CI   | <b>58</b>               | <b>2</b>             |   |                  |         |          |           |          |                            |                           |  |
|           |  | Blood glucose/ AND CVD/ CI  | <b>13</b>               | <b>1</b>             |   |                  |         |          |           |          |                            |                           |  |
|           |  | Myocardial infarction/ep,di AND NIDDM/ M  | <b>42</b>               | <b>3</b>             |   |                  |         |          |           |          |                            |                           |  |
|           |  | NIDDM/ AND CVD/ep, di M   | <b>14</b>               | <b>4</b>             |   |                  |         |          |           |          |                            |                           |  |

| QUESTIONS                              |  | KEY WORDS   | NO. ARTICLES IDENTIFIED | NO RELEVANT ARTICLES | ARTICLES IDENTIFIED BY OTHER STRATEGIES | TOTAL FOR REVIEW | LEVEL I | LEVEL II | LEVEL III | LEVEL IV | TOTAL NO REVIEWED & GRADED | HIGHEST LEVEL OF EVIDENCE |  |
|--|--|---|-------------------------|----------------------|---|------------------|---------|----------|-----------|----------|----------------------------|---------------------------|--|
| <b>2.</b>                              | <b>Who should be tested for undiagnosed Type 2 diabetes?</b> | CVD/ AND undiagnosed diabetes.mp M (96-99)                  | <b>5</b>                | <b>1</b>             |   |                  |         |          |           |          |                            |                           |  |
|  |  | NIDDM/ep, di AND Stroke/ M                                  | <b>29</b>               | <b>2</b>             |   |                  |         |          |           |          |                            |                           |  |
|  |  | NIDDM/ep, di AND (Hospitalisation/ OR patient admission/) M | <b>16</b>               | <b>4</b>             |   |                  |         |          |           |          |                            |                           |  |
|  |  | NIDDM/ AND (hospitalisation/ OR patient admission/) CI      | <b>4</b>                | <b>0</b>             |   |                  |         |          |           |          |                            |                           |  |
|  |  | NIDDM/ep, di AND Obesity/ M                                 | <b>307</b>              | <b>38</b>            |   |                  |         |          |           |          |                            |                           |  |
|  |  | NIDDM/ep, di AND Overweight/ M                              | <b>31</b>               | <b>2</b>             |   |                  |         |          |           |          |                            |                           |  |
|  |  | NIDDM/ep, di AND Ethnic groups/ M                           | <b>58</b>               | <b>11</b>            |   |                  |         |          |           |          |                            |                           |  |
|  |  | NIDDM/ep, di AND Family history/ M                          | <b>112</b>              | <b>21</b>            |   |                  |         |          |           |          |                            |                           |  |
|  |  | NIDDM/ep, di AND Parental diabetes M                        | <b>2</b>                | <b>1</b>             |   |                  |         |          |           |          |                            |                           |  |
|  |  | NIDDM/ep, di AND Smoking/ M                                 | <b>87</b>               | <b>18</b>            |   |                  |         |          |           |          |                            |                           |  |
|  |  | NIDDM/pa, di, ep, et, AND age of onset M (All yrs)          | <b>64</b>               | <b>0</b>             |   |                  |         |          |           |          |                            |                           |  |
| NIDDM/ AND age.mp AND risk M (all yrs) | <b>39</b>  | <b>2</b>  |                         |                      |   |                  |         |          |           |          |                            |                           |  |

| QUESTIONS |  | KEY WORDS  | NO. ARTICLES IDENTIFIED | NO RELEVANT ARTICLES | ARTICLES IDENTIFIED BY OTHER STRATEGIES | TOTAL FOR REVIEW | LEVEL I | LEVEL II | LEVEL III | LEVEL IV | TOTAL NO REVIEWED & GRADED | HIGHEST LEVEL OF EVIDENCE |  |  |
|-----------|--|--|-------------------------|----------------------|---|------------------|---------|----------|-----------|----------|----------------------------|---------------------------|--|--|
| <b>2.</b> | <b>Who should be tested for undiagnosed Type 2 diabetes?</b> | (Hypertension/ OR lipids/ OR age/ OR cardiovascular/ OR macrovascular.mp) AND blood glucose/ AND diabetes mellitus AND diabetes mellitus/epi/ NOT diabetes mellitus, insulin-dependent/ NOT prospective/ NOT gestational.mp M  | <b>745</b>              | <b>22</b>            |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | Blood glucose/ AND diabetes mellitus/ep AND gestational.mp M   | <b>114</b>              | <b>4</b>             |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | NDDM/ AND (birth weight/ OR birthweight.mp OR macrosomia.mp) M   | <b>101</b>              | <b>1</b>             |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | NIDDM/ep AND (ethnic group OR Family History OR Cigarette smoking OR smoking OR Cardiovascular disease OR obesity OR heart infarct OR stroke OR hospitalisation OR hosp admission OR age OR hypertension OR lipid OR sex OR cardiovascular risk OR vascular disease EM | <b>425</b>              | <b>9</b>             |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | NIDDM/ ep AND (prospective/ OR follow/) NOT mortality/   | <b>300</b>              | <b>10</b>            |   |                  |         |          |           |          |                            |                           |  |  |

| QUESTIONS |  | KEY WORDS  | NO. ARTICLES IDENTIFIED        | NO RELEVANT ARTICLES | ARTICLES IDENTIFIED BY OTHER STRATEGIES | TOTAL FOR REVIEW | LEVEL I | LEVEL II | LEVEL III | LEVEL IV | TOTAL NO REVIEWED & GRADED | HIGHEST LEVEL OF EVIDENCE |  |  |
|-----------|--|--|--------------------------------|----------------------|---|------------------|---------|----------|-----------|----------|----------------------------|---------------------------|--|--|
| 2.        | <b>Who should be tested for undiagnosed Type 2 diabetes?</b> | (Obesity/ OR BMI OR bodyweight OR overweight OR smoking/) AND NIDDM/ CI  | 64                             | 8                    |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | NIDDM/ep,di AND age factors/ CI  | 5                              | 0                    |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | NIDDM AND (Ethnic groups/ OR parental diabetes.mp OR age factors/) CI  | 26                             | 2                    |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | NIDDM/ AND age factors/ CO (all yrs)   | 13                             | 2                    |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | NIDDM/ AND (risk factors/ OR Smoking/ OR Obesity/ OR CVD/) CO  | 9                              | 0                    |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | (Cholesterol/ OR HDL cholesterol/ OR LDL cholesterol/ or VLDL cholesterol/ or lipid/ or hypercholesterolemia/ or triacylglycerol/ or hyperlipidemia) and NIDDM/ and risk factor/ EM, M, CI | 311 (EM)<br>456 (M)<br>14 (CI) | 22                   |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | NIDDM and (birthweight.mp or birthweight/ or fetal macrosomia) and risk factors M (all yrs)  | 20                             | 1                    |   |                  |         |          |           |          |                            |                           |  |  |
|           |  | NIDDM/ and (birthweight.mp OR birthweight/ OR fetal macrosomia) M (all yrs)  | 73                             | 2                    |   |                  |         |          |           |          |                            |                           |  |  |

| QUESTIONS |   | KEY WORDS  | NO. ARTICLES IDENTIFIED | NO RELEVANT ARTICLES | ARTICLES IDENTIFIED BY OTHER STRATEGIES | TOTAL FOR REVIEW | LEVEL I   | LEVEL II | LEVEL III | LEVEL IV  | TOTAL NO REVIEWED & GRADED | HIGHEST LEVEL OF EVIDENCE |
|-----------|---|--|-------------------------|----------------------|---|------------------|-----------|----------|-----------|-----------|----------------------------|---------------------------|
| 3.        | How should case detection and diagnosis testing for Type 2 diabetes be performed? | <b>Total for Questions 3&amp;4</b>   | <b>1183</b>             | <b>189</b>           | <b>0</b>                                | <b>131</b>       | <b>80</b> | <b>1</b> | <b>19</b> | <b>60</b> | <b>80</b>                  | <b>I</b>                  |
| 4.        | How often should testing be performed?  | Diabetes Mellitus, Non-Insulin-Dependent/ co AND diagnosis/ AND retinopathy/ AND (time/ OR month/ OR year/) AND english Language M | 72                      | 1                    |   |                  |           |          |           |           |                            |                           |
|           |   | American.mp AND Diabetes.mp AND Association.mp OR ADA.mp) AND "World Health Organization".mp OR WHO.mp M                           | 35                      | 6                    |   |                  |           |          |           |           |                            |                           |
|           |   | Mass screening/ AND Diabetes Mellitus, Non-Insulin-Dependent/ di, p M  | 74                      | 2                    |   |                  |           |          |           |           |                            |                           |
|           |   | Diabetes mellitus/ cl, di AND (haemoglobin a, glycosylated/ OR glucose/ OR fasting/ OR glucose tolerance test) M, CI(82-99)        | 33 (CI)<br>268 (M)      | 98                   |   |                  |           |          |           |           |                            |                           |
|           |   | (Glucose tolerance/ OR glcosylated hemoglobin/ OR fasting/) AND diabetes mellitus/ di EM   | 338                     | 75                   |   |                  |           |          |           |           |                            |                           |

| QUESTIONS |  | KEY WORDS  | NO. ARTICLES IDENTIFIED | NO RELEVANT ARTICLES | ARTICLES IDENTIFIED BY OTHER STRATEGIES | TOTAL FOR REVIEW | LEVEL I | LEVEL II | LEVEL III | LEVEL IV | TOTAL NO REVIEWED & GRADED | HIGHEST LEVEL OF EVIDENCE |
|-----------|--|--|-------------------------|----------------------|---|------------------|---------|----------|-----------|----------|----------------------------|---------------------------|
| 3.        | <b>How should case detection and diagnosis testing for Type 2 diabetes be performed?</b> | Reagent strips/ OR meter.mp CI   | 151                     | 1                    |   |                  |         |          |           |          |                            |                           |
|           |  | Blood glucose/ AND (reagent strips/ OR meter.mp) AND diabetes mellitus/ M (all yrs)                  | 159                     | 3                    |   |                  |         |          |           |          |                            |                           |
| 4.        | <b>How often should testing be performed?</b>  | (Glucose blood level/ AND test strip/) OR (blood glucose level/ AND meter/) AND diabetes mellitus/EM | 53                      | 3                    |   |                  |         |          |           |          |                            |                           |