Is there a Link between Components of Health-Related Functioning and Incident Impaired Glucose Metabolism and Type 2 Diabetes? The Australian Diabetes Obesity and Lifestyle study (AusDiab)

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**Aim:** To determine the longitudinal association of components of health related functioning (HRF) with incident impaired glucose metabolism and type 2 diabetes mellitus (DM).

**Methods:** The Australian Diabetes Obesity and Lifestyle study (AusDiab) is a national, longitudinal study of adults aged ≥25 years from 42 randomly selected areas of Australia. Diabetes status was defined using the World Health Organization criteria and HRF was assessed using the SF-36 questionnaire in 1999-2000 and 2004-2005.

**Results:** Incident impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and newly diagnosed type 2 diabetes mellitus (NDM) were associated with increased bodily pain (BP) at baseline compared to those with normal glucose tolerance (NGT) (IFG p=0.005, IGT p<0.004, NDM p=0.005), after adjustment. Additionally, those with incident IGT and NDM had significantly reduced physical functioning (PF), general health (GH), mental health and vitality (VT) at baseline compared to those with NGT. After controlling for factors associated with incident diabetes, those in the lowest quartile of the physical component summary scale at baseline had at least a 50% higher risk of progression to impaired glucose metabolism and diabetes 5 years later.

**Conclusions:** These findings show that incident IFG, IGT and NDM are associated with reduced HRF independent of CVD and that this is evident prior to the onset of these conditions. If future health promotion campaigns are to effectively target those at high risk of developing diabetes, an understanding of the process of declining health prior to the onset of the disease is essential.
Type 2 diabetes is increasing rapidly throughout the world. The difficulties in curbing this trend make it vital that we fully understand all aspects of the disease process. While traditional risk factors for type 2 diabetes mellitus (DM) have been extensively studied, the role of components of health realted functioning (HRF), an important component of health(1), has not fully been explored in contemporary, population-based studies.

There is now growing evidence to suggest that HRF, which reflects a measure of physical, social and mental health functioning, may be impaired prior to the onset of type 2 DM(2). A small number of cross-sectional studies have suggested that those with impaired fasting glucose (IFG) and or impaired glucose tolerance (IGT) have reduced HRF compared to those with normal glucose tolerance (NGT) on a number of the SF-36 dimensions (3-5). While many studies have previously shown that people with diabetes-related complications have reduced HRF compared to those without complications (6; 7) and several studies have shown that HRF is impaired among those with DM compared to those without DM (8; 9), little is known about the stage of the disease at which HRF becomes impaired. This is important to establish if a holistic approach to health care is to be taken and we are to fully understand the aetiology and pathogenesis of the disease.

An understanding of how some psychosocial factors directly impact on the development of type 2 DM and other chronic diseases is already beginning to emerge. Psychosocial stress for example is known to increase the inflammatory process(10; 11) and has been linked directly with accelerated atherosclerosis(10), myocardial ischemia(12) and incident type 2 DM(2). This suggests that psychosocial risk factors are likely to be important to consider in the identification of individuals at high risk of developing type 2 DM, as well as in interventions to prevent diabetes. The Australian Diabetes, Obesity and Lifestyle study (AusDiab), with its large, national, population-based sample, with 5 years of follow-up, provides an ideal setting in which to investigate the association of HRF with the subsequent development of impaired glucose metabolism and type 2 DM.

**PATIENTS AND METHODS**

**Study Population:** The population, methods and response rates of the AusDiab study are detailed elsewhere (13; 14). In brief, the AusDiab study was a population-based study of 11,247 people age ≥25 years, from 42 randomly selected urban and rural areas of Australia, conducted in 1999-2000. At baseline, 55.3% (n=11,247) of those completing a household questionnaire undertook the full survey, and the follow-up response rate in 2004-2005 was 60.6% (6537/10788). There were 459 who were ineligible for the follow-up study due to a terminal illness, death or because they had refused further contact. The study was approved by the ethics committee of the International Diabetes Institute. Informed consent for the study was obtained from all participants.

Diabetes classification was based on plasma glucose results, using the 1999 WHO diabetes classification (15). Diabetes was diagnosed on the basis of fasting plasma glucose of ≥7.0mmol/l or 2-h plasma glucose of ≥11.1mmol/l or current treatment with insulin or oral hypoglycaemic medication. Those with self-reported diabetes, those on current treatment (insulin or oral hypoglycaemic medication) or with diabetic glucose values at baseline, were categorized as having known diabetes (KDM) and were excluded from this study. Participants diagnosed with diabetes through the AusDiab study were categorised as newly diagnosed diabetes (NDM). Incident newly diagnosed diabetes (incident DM) at 5
years was defined as persons without KDM or NDM at baseline who were diagnosed with diabetes by the follow-up examination (N=224). Incident IGT and IFG were defined at five years as persons with NGT at baseline that were diagnosed with IGT or IFG at the 5 year follow-up examination (n=432). Only those with NGT at baseline and follow-up (n=4225) were included in the comparison group for the analyses focused on categories of glucose metabolism. For these analyses, complete data were available on key variables of interest for 200 with incident NDM, 257 with incident IGT, 137 with incident IFG and 3906 who remained in the NGT throughout. For the analysis focused on those with and without incident NDM those with IFG and IGT at baseline were additionally included.

In 1999–2000, FPG and 2hPG levels were determined by a glucose oxidase method using an Olympus AU600 automated analyser (Olympus Optical Co. Ltd, Tokyo, Japan), and in 2004–2005, a spectrophotometric-hexokinase method utilising a Roche Modular (Roche Diagnostics, Indianapolis, USA) was used. Re-measurement of stored baseline samples on the assay used at follow-up showed good agreement between the two assays(14). Serum triglycerides, total cholesterol and high density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods at baseline. Total glycated hemoglobin analysis used high performance liquid chromatography (Bio-Rad Variant Haemoglobin Testing System, Bio-Rad, Hercules, CA, USA) with standardized conversion to HbA1c values (normal range 4.2–6.3%). C-peptide was measured by radioimmunoassay with Linco human c-peptide kits (Linco, St. Charles, MO). Blood pressure was measured using Dinamap or a standard mercury sphygmomanometer. To account for any effect due to differential measurement error, manual blood pressure measurements were adjusted as previously described(16). Hypertension was defined as present if systolic blood pressure (SBP) was ≥140mmHg, diastolic blood pressure (DBP) ≥90mmHg or the participant reported current treatment for hypertension. Height and weight were measured in light clothing by a trained observer. Body mass index (BMI) was calculated as weight (kg) / height (m²). Information on smoking, medication and history of diabetes were obtained by interview.

Components of social functioning were assessed using version 1 of the SF-36 Quality of Life Scale (17). The SF-36 (http://www.sf-36.org/tools/sf36.shtml) is a self-administered measure of perceived health status over the past week, comprising eight domains: Physical Functioning (PF), Role-Physical (RF), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), and Mental Health (MH). Items for each dimension are coded, summed and translated from worst health (0) to best health (100). Physical functioning refers to the ability to perform activities (walking, climbing stairs, bending and stretching, lifting and carrying objects) without limitation. Role limitation (physical) refers to the limitations that reduced physical health has on the range and extent of physical activities one is able to perform. Bodily pain refers to the severity of pain and its impact on daily activities. General health is a rating of one’s own health, a comparison with others health and proneness to illness. Vitality refers to how energetic or tired a person feels. Social functioning refers to the impact of physical and emotional health on the ability to perform normal social activities. Role limitation (emotional) refers to limitations that emotional problems put on the range and extent of activities one could perform. Mental health refers to the degree of nervousness or calmness, happiness or sadness.

The survey additionally established scores for two summary measures - Physical components summary (PCS) and Mental health component
summary (MCS)(17). PCS is a summary of PF, RP, BP and GH. The MCS is a summary measure of VT, SF, RE and MH. Both PCS and MCS are components of health which have been shown to be useful and valid measures of mental and physical health functioning relative to health profile. Overall, the SF-36 has been widely used in studies of chronic disease.

**Statistical Methods:** Statistical analysis was performed using SPSS v14.0 for Windows (SPSS Inc., 2005, Chicago, IL). Descriptive information for each of the variables was derived and distribution assessed. Univariate associations between each dimension of the SF-36 scale and other variables of interest were assessed using ANOVA for metric variables and a chi-squared test for categorical variables. Two multivariate models (ANCOVA), applied separately to each SF-36 scale, allow tiered analysis of the effect of diabetes status on quality of life measures. Model 1 was adjusted for age and sex only. Model 2 added three further important factors to model 1 - systolic blood pressure, BMI and total cholesterol. Model 3 - SF-36 dimensions adjusted for model 2 & smoking, known cardiovascular disease and medication for hypertension or a lipid abnormality. Marginal means are presented for each model, representing the mean values for each SF-36 scale after adjustment for covariates. A p value of <0.05 was considered statistically significant. The risk of being in the lowest quartile (i.e. poor quality of life) of each summary measure (physical and mental component of health) was assessed using logistic regression.

**RESULTS**
The study included 4500 participants with data available on the SF-36 questionnaire. The characteristics of the population according to glucose tolerance status at outcome are shown in table 1. Across categories of glucose metabolism there were significant differences in age, systolic and diastolic blood pressure, cholesterol, triglycerides, glycaemic measures, waist circumference and BMI. Incident diabetes at follow-up was associated with significantly lower mean baseline scores on each of the 8 SF-36 dimensions compared to those who remained in the NGT category, adjusted for age and sex (FP, RF, BP, GH, vitality, SF, role limitation: emotional and mental health) (table 2). These differences were only partially attenuated by adjustment for BMI, systolic blood pressure and total cholesterol at baseline. Further adjustment for known CVD, smoking, lipid and hypertension reduced the mean values of each dimension, but did not significantly alter the association. Among those with incident IGT at follow-up, baseline scores for PF, RP, BP, GH, vitality, SF and MH were significantly lower compared to those with NGT (after adjustment for age and sex). These differences in PF, BP, GH, vitality, and MH were only partially attenuated by adjustment for systolic blood pressure, BMI and total cholesterol. Further adjustment for known CVD, smoking, lipid and hypertension reduced the mean values of each dimension, but did not significantly alter the association. Among those with incident IFG at follow-up, baseline scores for PF, RP and BP were significantly lower compared to those with NGT. However after further adjustment for BMI, systolic blood pressure and total cholesterol at baseline only the difference for BP remained. Further adjustment for known CVD, smoking, lipid and hypertension reduced the mean values of each dimension, but did not significantly alter the association. Further inclusion of baseline FPG in a fifth model failed to attenuate the associations observed for each dimension of the SF-36 (data not shown). A final model comparing those with and without incident DM (using all available data n=5450) made no difference to the association of DM with impaired quality of life on the PF, BP, GH, SF and RE
dimensions (after adjustment for age, sex, BMI, total cholesterol, smoking, known CVD and medication for hypertension or a lipid abnormality. PF mean (M) and standard error (SE) for PF: no DM 78.5 (0.6) and DM 74.9 (1.2). p=0.002; RP – no DM 75.9 (1.1), DM 71.9 (2.4), p=0.070; BP – no DM 71.6 (0.8), DM 68.4 (1.6), p=0.043; GH – no DM 64.7 (0.6), DM 61.2 (1.3), p=0.004; VT – no DM 59.3 (0.7), 57.0 (1.5), p=0.104; SF – no DM 84.6 (0.7), DM 81.0 (1.4), p=0.006; RE – no DM 82.1 (1.1), DM 77.9 (2.3), p=0.051; MH – no DM 74.8 (0.6) DM 72.8 (1.2), p=0.096.

The physical functioning summary score showed a significant gradual decrease across categories of glucose metabolism from NGT through to incident diabetes (Figure 1). After controlling for factors associated with incident diabetes, those in the lowest quartile of the physical component summary scale at baseline had at least a 50% higher risk of progression to impaired glucose metabolism and diabetes 5 years later (odds ratios (OR) for: IFG 1.7, 95% confidence intervals (CI), 1.2-2.5; IGT 1.5 (CI 1.1-2.1); NDM 1.5 (CI 1.1-2.1)). An association only with NDM was evident for the mental health component summary measure.

DISCUSSION
There were three principal findings in this national, population-based study from Australia. Firstly, those with incident IFG had increased bodily pain prior to the onset of IFG. Secondly, those with IGT had increased bodily pain, reduced physical functioning, general health, vitality and mental health prior to the onset of IGT. Thirdly, those with incident NDM had increased bodily pain, reduced physical functioning and general health prior to the onset of type 2 DM. These are important findings. The impact of HRF on subsequent development of incident impaired glucose metabolism and type 2 DM, as far as we are aware, has not previously been explored in a large national representative population based sample. The identification of impaired HRF factors prior to the onset of impaired glucose metabolism and NDM suggest HRF is likely to be important in the identification of individuals at high risk of type 2 DM.

Our study results can be compared with the few population-based studies available (3; 4). In a cross-sectional Australian study of 4060 people, those with IFG had significantly worse scores for physical functioning and bodily pain compared to those with NGT (after adjustment for age, sex and cardiovascular disease) (4). While the AusDiab cross-sectional study showed no impairment in HRF among those with IFG compared to those with NGT, those with IGT had impaired physical and social functioning compared to those with NGT (after adjustment for age, sex, BMI, physical activity and treatment for hypertension or a lipid abnormality) (5). In a study by Hiltunen et al, a pattern of general worsening of HRF across categories of glucose tolerance status was evident. However, due to the limited sample size, no firm conclusions could be drawn (3). In the present study, those with incident NDM had worse scores on all SF-36 dimensions apart from mental health when compared to those with NGT. This is very similar to the findings of the study by Chittleborough et al (4) which showed that HRF was impaired on all dimensions of the HRF scale compared to those with NGT. A consistent finding through the limited number of studies to assess HRF across the spectrum of glycaemic values is that the decline in HRF is related to the physical component of the SF-36, with mixed results shown for the mental health component (3-5). A similar pattern has been observed in research focused on HRF with adiposity, coronary heart disease, and insulin resistance (18-22). It is likely that inactivity is a risk factor for both impaired HRF and impaired glucose metabolism and type 2 DM. In terms
of physical functioning, metabolic abnormalities underpinning type 2 DM have been associated with reduced muscle strength and impaired HRF in the domain of physical functioning. In a large prospective study assessing body weight and HRF, the study showed that after four years, weight gain was associated with decreased physical functioning, vitality and increased bodily pain, regardless of baseline weight status(23). In contrast, those who lost weight had increased physical functioning and vitality and decreased bodily pain. Identification of people with mild to moderately impaired physical functioning could provide some prognostic information on the future risk of DM very early in the disease process. This is particularly relevant as it is well established that there is a strong link between physical inactivity, obesity and type 2 DM. Given improved HRF among those with DM is known to improve self management and lead to lifestyle changes, crucial for improved glycaemic control, HRF across the continuum of glycaemic values requires further investigation(24).

The findings from this study raise questions about the casual pathways and mechanisms involved in diabetes onset and its progression related to HRF and other salient psychosocial determinants. For example, the presence of reduced HRF in the preceding years to disease onset may suggest that the process is mediated through the behavioural pathways known to reduce HRF and act as risk factors for chronic disease (eg increased sedentary behaviour as a result of reduced functioning). Although data from epidemiological cohort studies have previously refuted the suggestion that associations between psychosocial factors and disease risk are likely to be mediated through behavioral pathways(25), further research is required into the psychosocial determinants of chronic disease onset to provide a clearer picture of the associated casual pathways.

The current study has limitations. The follow-up response rate for the AusDiab was limited and this may have lead to an underestimation of the association between quality of life measures and glucose metabolism. The results of this study suggest there is an independent association between impaired HRF and IFG, IGT and NDM. It should be noted that this association is likely to be bidirectional. For example, among those with known DM, the presence of complications is associated with a reduced HRF and the greater the number or severity of complications the greater the decrease in HRF. This could be a consequence of having a number of complications decreasing quality of life or conversely the impact of poor HRF on diabetes control.

CONCLUSIONS
These findings show that IFG and IGT and NDM are associated with a reduced HRF and that this is evident prior to the onset of these conditions, independent of known CVD. This is an important finding. If future health promotion campaigns are to effectively target those at high risk of developing DM, an understanding of the process of declining health prior to the onset of the disease is essential.

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**Figure Legends:**

Figure 1a  Physical Components Summary Scale of AusDiab study participants according to diabetes status at the 5 year follow-up.

Figure 1 b  Mental Health Components Summary Scale of AusDiab study participants according to diabetes status at the 5 year follow-up.

NDM - newly diagnosed diabetes; IFG - impaired fasting glucose; IGT - impaired glucose tolerance; NGT - normal glucose tolerance. Error bars represent 95% confidence intervals. Model 1 adjusted for age and sex, model 2 adjusted for age, sex, BMI, systolic blood pressure and total cholesterol. Model 3 adjusted for age, sex, BMI, systolic blood pressure, total cholesterol, current treatment for hypertension or lipid abnormalities and known CVD. Physical component score is a summary of physical function, role physical, bodily pain and general health. The Mental Health Component summary scale is a summary measure of vitality, social function, role emotional and mental health.
REFERENCES


Table 1. Baseline population characteristics of the AusDiab study participants according to diabetes status at the five year follow-up*

<table>
<thead>
<tr>
<th></th>
<th>Analysis of incident IFG/IGT</th>
<th>Analysis of incident DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NGT – ‘99 &amp; ‘05</td>
<td>Incident IFG</td>
</tr>
<tr>
<td>N</td>
<td>3906</td>
<td>137</td>
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<tr>
<td>Age (years)</td>
<td>49 (12)</td>
<td>51 (10)</td>
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<tr>
<td>Sex (Male)</td>
<td>43</td>
<td>58</td>
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<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.2 (0.4)</td>
<td>5.6 (0.3)</td>
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<td>2 Hour plasma glucose (mmol/l)</td>
<td>5.4 (1.1)</td>
<td>5.7 (1.2)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>25.9 (4.3)</td>
<td>28.8 (4.6)</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>87.4 (12.7)</td>
<td>97.5 (11.8)</td>
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<td>Lipid treatment (%)</td>
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<td>7</td>
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<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.5 (0.4)</td>
<td>1.3 (0.3)</td>
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<tr>
<td>Total Cholesterol (mmol/l)</td>
<td>5.6 (1.0)</td>
<td>5.8 (0.9)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.1 (0.8 - 1.6)</td>
<td>1.4 (1.0 - 2.2)</td>
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<tr>
<td>Current smoker (%)</td>
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<td>10</td>
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<tr>
<td>Hypertension (%)</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>125 (16)</td>
<td>131 (17)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>69 (11)</td>
<td>73 (11)</td>
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</table>

Data given as mean (standard deviation). *Only those with complete data on variables modeled are included. † Includes those with IFG or IGT at baseline or follow-up. IFG – Impaired fasting glucose. IGT – Impaired glucose tolerance, NDM – newly diagnosed DM. Those with NGT had normal glucose tolerance at baseline and follow-up. Those included with incident IFG or IGT had NGT at baseline. Those with incident DM were free of DM at baseline and had a diagnosis of newly diagnosed DM at follow-up.
Table 2. Adjusted mean values of baseline SF-36 dimensions according to glucose tolerance status at five years: the AusDiab study

<table>
<thead>
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<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<td>SF-36 dimensions adjusted for diabetes status, age &amp; sex</td>
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<td>SF-36 dimensions adjusted for model 2 &amp; smoking, known cardiovascular disease and medication for hypertension or a lipid abnormality</td>
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<td>Marginal mean (SE)</td>
<td>P value</td>
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<tr>
<td>NGT ‘99 &amp; ‘05</td>
<td>86.5 (0.3)</td>
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<td>Incident IFG</td>
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<td>0.010</td>
<td>85.1 (1.3)</td>
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<td>Incident IGT</td>
<td>82.7 (1.0)</td>
<td>&lt;0.001</td>
<td>84.2 (1.1)</td>
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<td><strong>Role limitation physical</strong></td>
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<td>NGT ‘99 &amp; ‘05</td>
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<td>REF</td>
<td>89.4 (0.3)</td>
</tr>
<tr>
<td>Incident IFG</td>
<td>87.0 (1.5)</td>
<td>0.105</td>
<td>87.5 (1.5)</td>
</tr>
<tr>
<td>Incident IGT</td>
<td>87.0 (1.1)</td>
<td>0.035</td>
<td>87.4 (1.1)</td>
</tr>
<tr>
<td>Incident NDM</td>
<td>83.8 (1.3)</td>
<td>&lt;0.001</td>
<td>84.5 (1.3)</td>
</tr>
<tr>
<td><strong>Role limitation: emotional</strong></td>
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<tr>
<td>Diabetes status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGT ‘99 &amp; ‘05</td>
<td>86.5 (0.5)</td>
<td>REF</td>
<td>86.5 (0.5)</td>
</tr>
<tr>
<td>Incident IFG</td>
<td>83.0 (2.5)</td>
<td>0.153</td>
<td>83.8 (2.5)</td>
</tr>
<tr>
<td>Incident IGT</td>
<td>83.7 (1.8)</td>
<td>0.128</td>
<td>84.3 (1.8)</td>
</tr>
<tr>
<td>Incident NDM</td>
<td>79.8 (2.1)</td>
<td>0.001</td>
<td>80.8 (2.1)</td>
</tr>
<tr>
<td><strong>Mental Health</strong></td>
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<td>Diabetes status:</td>
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<td></td>
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<tr>
<td>NGT ‘99 &amp; ‘05</td>
<td>77.3 (0.3)</td>
<td>REF</td>
<td>77.2 (0.3)</td>
</tr>
</tbody>
</table>
Incident IFG  75.7 (1.4)  0.243  75.9 (1.4)  0.356  74.4 (1.5)  0.326
Incident IGT  74.2 (1.0)  0.003  74.4 (1.0)  0.007  73.1 (1.2)  0.009
Incident NDM  74.3 (1.1)  0.011  74.7 (1.1)  0.028  73.5 (1.3)  0.051

**Figure 1a. Physical Components Summary Scale of AusDiab study participants according to diabetes status at the 5 year follow-up.**

![Graph showing odds ratio for different glucose metabolism categories across different models.](image-url)
Figure 1b. Mental Health Components Summary Scale of AusDiab study participants according to diabetes status at the 5 year follow-up.

**Categories of glucose metabolism**

NDM - newly diagnosed diabetes; IFG - impaired fasting glucose; IGT - impaired glucose tolerance; NGT - normal glucose tolerance. Error bars represent 95% confidence intervals. Model 1 adjusted for age and sex, model 2 adjusted for age, sex, BMI, systolic blood pressure and total cholesterol. Model 3 adjusted for age, sex, BMI, systolic blood pressure, total cholesterol, current treatment for hypertension or lipid abnormalities and known CVD. Physical component score is a summary of physical function, role physical, bodily pain and general health. The Mental Health Component summary scale is a summary measure of vitality, social function, role emotional and mental health.