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How to approach management of the patient with obesity and prediabetes

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Medical science has made such tremendous progress that there is hardly a healthy human left.

— Aldous Huxley —

	Total diabetes	Diagnosed diabetes†	Undiagnosed diabetes‡	Percent undiagnosed	Prediabetes§	Mean body mass index, kg/m²
Overall	14.3 (12.2-16.8)	9.1 (7.8-10.6)	5.2 (4.0-6.9)	36.4 (30.5-42.7)	38.0 (34.7-41.3)	28.7 (28.3-29.2)
Age Group	p<0.001	p<0.001	p<0.001	p=0.08	p<0.001	p=0.007
20-44 years of age	5.0 (3.8-6.7)	2.7 (2.0-3.6)	2.4 (1.6-3.6)	47.0 (37.1-57.0)	28.2 (24.4-32.4)	28.1 (27.6-28.6)
45-64 years of age	17.5 (14.4-21.0)	11.6 (9.5-14.0)	5.8 (4.0-8.5)	33.5 (25.0-43.3)	44.9 (37.6-52.4)	29.5 (28.8-30.3)
≥65 years of age	33.0 (27.1-39.4)	21.3 (18.1-24.9)	11.6 (8.3-16.1)	35.3 (28.8-42.4)	49.5 (43.4-55.6)	28.5 (27.7-29.2)
Sex	p=0.66	p=0.54	p=0.90	p=0.91	p=0.20	p=0.07
Men	14.7 (12.0-17.7)	9.4 (8.2-10.7)	5.3 (3.5-7.8)	36.1 (28.1-44.9)	39.8 (35.6-44.1)	28.5 (28.0-29.0)
Women	14.0 (11.6-16.9)	8.9 (7.2-10.9)	5.1 (3.7-7.1)	36.7 (28.9-45.2)	36.3 (32.0-40.8)	28.9 (28.4-29.4)

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Outline

- Case history
- For and against screening for diabetes and diagnosing prediabetes
- Definitions and prevalence
- Risks of impaired glucose metabolism
- Guidelines for screening and diagnostic criteria
- Lifestyle interventions for prevention
- Pharmacological Interventions for prevention
- Case History

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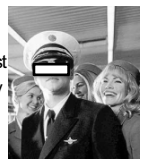
Case History

- JG is a 54 yr. old Caucasian commercial airline pilot
- He has passed his airline certification 6 months' ago
- He falls and sustains a Colles' fracture of his left wrist
- On admission to the fracture clinic, he has a capillary blood glucose measured
- The result is 5.7 mmol/l (104 mg) and he is told that he should see his doctor as he has pre-diabetes
- His father and brother both developed type 2 diabetes in their 70's
- He has a BMI of 30 $kg.m^{-2}$



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Case History

- Do you agree that he has pre-diabetes?
- If he does will this stop him flying?
- Are there further tests that you would want to do?
- If these confirm a diagnosis of pre-diabetes would you treat him with
  - Advice on diet and exercise
  - Metformin
  - Other hypoglycaemic medication
  - Weight loss medication

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Why diagnose pre-diabetes?

- It might explain a patient's symptoms?
- It is a risk for ill health in itself
- It is a risk for developing type 2 diabetes
- Early treatment provides benefit
  - Prevents development of diabetes
  - Delays development of diabetes
  - Reduces CV morbidity and mortality
- Unproven benefit but seems logical in the same way that other risk factor lowering (lipids, BP) has been proven to be beneficial

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Why not diagnose pre-diabetes?

- Implications for individuals include:
  - the time and other resources necessary to undergo the screening test (or tests) and any subsequent diagnostic test (or tests);
  - the psychological and social effects of the results whether the screening test proves 'positive' or 'negative' and whether or not the diagnosis of type 2 diabetes is subsequently made and
  - the adverse effects and costs of earlier treatment of type 2 diabetes or of any preventive measures instituted as a result of the individual being found to have diabetes. These may include occupational discrimination and/or increased costs or difficulty in obtaining insurance.

Screening for Type 2 Diabetes Report of a World Health Organization and International Diabetes Federation meeting 2003 WHO/NMH/MNC/03.1. http://www.who.int/diabetes/publications/en/screening_mnc03.pdf

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Why not diagnose pre-diabetes?

- The effects on the health system and society as a whole:
  - costs and other implications (especially in primary care and support services such as clinical biochemistry) of carrying out the screening test (or tests) and the necessary confirmatory test (or tests);
  - additional costs of the earlier treatment of those …at high risk of developing diabetes or cardiovascular disease in the future
  - the implications of false negative and false positive
  - loss of production as a result of the earlier diagnosis of the condition (from absence from work or reduced job opportunities, for example)

Screening for Type 2 Diabetes: Report of a World Health Organization and International Diabetes Federation meeting 2003 WHO/NMH/MNC/03.1. http://www.who.int/diabetes/publications/en/screening_mnc03.pdf

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Arguments against diagnosing pre-diabetes

- Population measures of glycaemia are continuous, with no inflections to provide obvious cut-off points
- Cut-offs for the diagnosis of diabetes are based on thresholds for risk of retinopathy
- Lesser degrees of hyperglycaemia increase the risk of developing diabetes and maybe arterial disease. But in both cases the risk is graded, making any choice of cut-off point purely arbitrary

Yudkin and Montori. BMJ. 2014; 349: g4485

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Arguments against diagnosing pre-diabetes

		Diabetes			Arterial disease		Retinal disease
	Predicts	Effect of lifestyle interventions	Effect of drugs	Predicts	Effect of lifestyle interventions	Effect of drugs	Predicts
Impaired glucose tolerance (7.8-11.1 mmol/L)*	+++	+++ (delays) + (prevents)	+++ (disguises) + (prevents)			?	+
Impaired fasting glucose (6.1-6.9 mmol/L)	++	?	(+)†	+	?	?	?
Expanded impaired fasting glucose (5.6-6.9 mmol/L)	+	?	?	+	?	?	?
Borderline HbA_{1c} (6.0-6.4%)	++	?	?	+	?	?	?
Expanded borderline HbA_{1c} (5.7-6.4%)	+	?	?	+	?	?	?

Yudkin and Montori. BMJ. 2014; 349: g4485

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Arguments against diagnosing pre-diabetes

- The logic of creating a diagnostic category of pre-diabetes is that it can provide benefit by precisely identifying those who will develop diabetes, but
  - Of 94 risk prediction models for diabetes, less than half included a measure of glycaemia
  - even with the best predictor, **impaired glucose tolerance**, more than half of people identified will be free of diabetes 10 years later and two thirds of people with **impaired fasting glucose** will not have diabetes after 10 years
  - 22 studies of lifestyle interventions through routine healthcare programmes for diabetes prevention found a mean weight loss of 2.1 kg. < ½ the 5.6 kg reported in the US Diabetes Prevention Program

Yudkin and Montori. BMJ. 2014; 349: g4485

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Cut-points for diagnosing diabetes, impaired glucose tolerance, and impaired fasting

Diagnosis	Venous plasma [a] mmol/L (mg/dL)	Venous blood mmol/L (mg/dL)	Capillary blood mmol/L (mg/dL)
IFG–FG	6.1 (110)	5.0 (90)	5.6 (101)
IGT–2hG	7.8 (140)	6.5 (117)	7.2 (130)
Diabetes–FG	7.0 (126)	5.8 (104)	6.5 (117)
Diabetes–2hG	11.1 (200)	9.4 (169)	10.3 (185)

FPG =fasting plasma glucose; FG=Fasting Glucose; IFG=impaired fasting glucose; IGT =impairedglucose tolerance; 2hG=2-h post-load glucose; 2hPG=2-h post-load plasma glucose

Ryden et al. European Heart Journal(2013) 34,3035-3087

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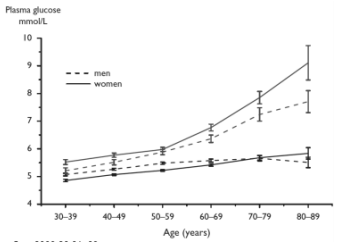
Diagnosis of prediabetes

IFG	IGT	HbA1c
≥5.6 to ≤6.9 mmol/L ≥100 to ≤125 mg/dL	≥7.8 to ≤11.0 mmol/L ≥140 to ≤199 mg/dL	≥5.7 to ≤6.4%
At screening	At screening	At screening

HbA_{1c}, glycosylated haemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance

American Diabetes Association. *Diabetes Care* 2010;33:S11-61.

DECODE*: fasting plasma glucose and 2 hr blood in 13 European population-based cohorts included



*Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe

Diabetes Care 2003;26:61–69

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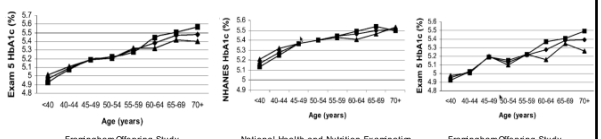
Effect of Aging on A1C Levels in Individuals Without Diabetes



Framingham Offspring Study Non-diabetic | National Health and Nutrition Examination Survey 2001–2004 Non-diabetic | Framingham Offspring Study Normal glucose tolerance

Pani et al. Diabetes Care 31:1991-1996,2008

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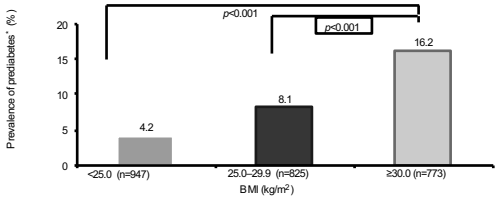
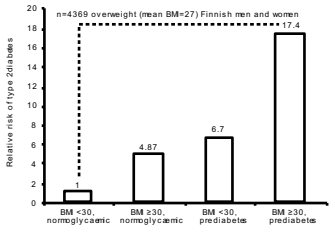
Overweight and obesity are major risk factors for prediabetes



Self-reported, physician-diagnosed, determined by the affirmative answer to the question: "Have you ever been told by a doctor that you have prediabetes?" *Prevalence figures are likely to be an underestimate, as prediabetes is largely undiagnosed. BMI, Body Mass Index

Hoster AS. *Prev Chronic Dis* 2009;6:A48.

Obese people with pre-diabetes (Impaired Glucose Regulation*) have 17 times as great a risk of type 2 diabetes

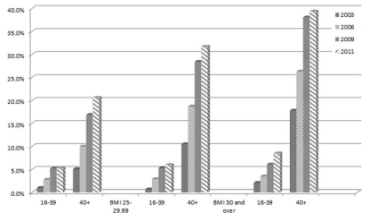


Hu et al. *Arch Intern Med*. 2004;164:892–6

*IGR: fasting plasma glucose 110-126 mg/dL or 2-hour plasma glucose 140-200 mg/dL

Prevalence of prediabetes* in England from 2003 to 2011: BMI and age

HbA1c cut-offs as specified by the American Diabetes Association, 5.7–6.4%



Mainous III AG et al. BMJ Open 2014;4:e005002 dd:10.1136/bmjopen-2014-005002

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Prevalence of prediabetes in England from 2003 to 2011: Odds Ratios for pre-diabetes

	2003	2011
Variable	OR (95% CI)	OR (95% CI)
Gender		
Female	1.00	1.00
Male	0.96 (0.83 to 1.12)	1.07 (0.91 to 1.25)
Age, years		
16–39	1.00	1.00
40+	6.82 (5.39 to 8.73)	4.871 (4.05 to 5.89)
Ethnicity		
White	1.00	1.00
South Asian	1.98 (1.36 to 2.83)	1.67 (1.12 to 2.50)
Black	2.28 (1.29 to 3.88)	1.45 (0.92 to 2.27)
Mixed/other	0.97 (0.37 to 2.10)	0.80 (0.57 to 1.11)

	2003	2011
Variable	OR (95% CI)	OR (95% CI)
BMI		
Less than 25	1.00	1.00
25–29.99	1.41 (1.16 to 1.72)	1.21 (1.00 to 1.45)
30 or over	2.62 (2.13 to 3.22)	1.71 (1.39 to 2.11)
High blood pressure diagnosis		
Normal/low	1.00	1.00
High	1.59 (1.35 to 1.87)	1.60 (1.33 to 1.92)
Social deprivation		
First quintile (least deprived)	1.00	1.00
Second quintile	1.23 (0.97 to 1.56)	0.92 (0.72 to 1.17)
Third quintile	1.17 (0.92 to 1.49)	1.11 (0.86 to 1.42)
Fourth quintile	1.62 (1.26 to 2.07)	1.45 (1.21 to 1.88)
Fifth quintile	1.13 (0.89 to 1.43)	1.00 (0.79 to 1.26)

Mainous III AG et al. BMJ Open 2014;4:e005002 dd:10.1136/bmjopen-2014-005002

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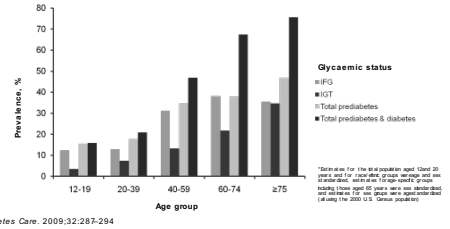
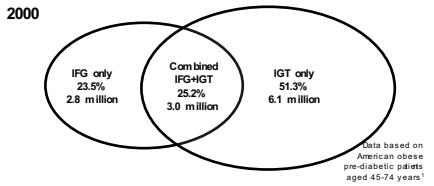
Standardized* prevalence of IFG, IGT, total pre-diabetes, and total diabetes and pre-diabetes, NHANES 2005–2006



*Estimates for the total population aged 12and 20 years and for racial/ethic groups average and sex standardized; estimates for age-specific groups including those aged 65 years were sex standardized, and estimates for sex groups were age standardized (all using the 2000 U.S. Census population)

Cowie et al. *Diabetes Care*. 2009;32:287-294

Relative proportions of IGT and IFG in pre-diabetic patients: 2000 and 2010



2010 USA prediabetes estimates: 35% >20y, 50% >65y } 79 million[2]

[1]Benjamin et al. *Diabetes Care*. 2003;26:645-9
[2]CDC 2011 National Diabetes Fact Sheet. http://www.cdc.gov/diabetes/pubs/estimates11.htm#7

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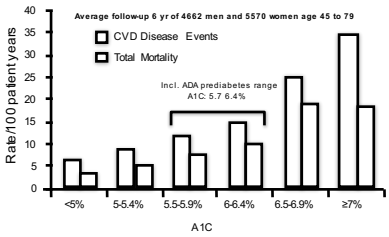
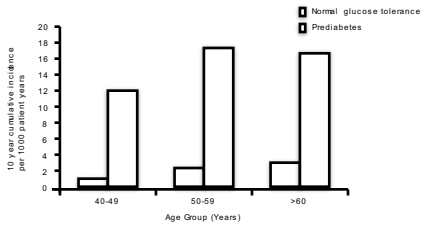
Impact of increased A1C on CV event and mortality in non-diabetic men (EPIC Norfolk)



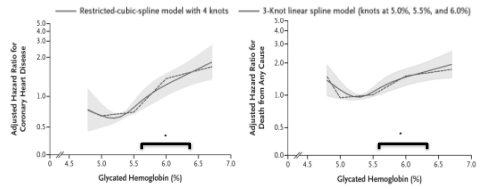
Khaw et al. *Ann Intern Med*. 2004;141:413-20

Pre-diabetes conversion rates



Forouhi et al. *Diabet Med*. 2007;24:200-7.

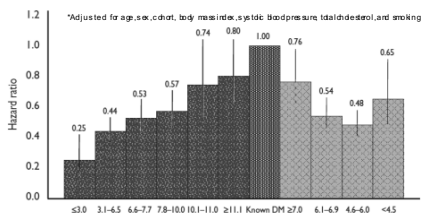
Association between A1C, coronary heart disease and mortality



Hazard ratios adjusted for: age, sex, race, LDL- HDL-cholesterol, ln-transformed triglyceride, BMI, waist-to-hip ratio, hypertension, family history of diabetes, education, alcohol use, physical-activity, smoking status
*ADA prediabetes range, A1C: 5.7 6.4%

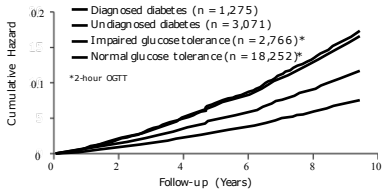
Selvin et al. *N Engl J Med*. 2010;362:800-11

Hazard ratios* for CVD mortality for FPG (□) and 2hPG (□) intervals using previously diagnosed DM (□) as reference category.



CVD, cardiovascular disease; DM, diabetes mellitus; FPG, fasting plasma glucose; 2hPG, 2-h post-load plasma glucose
Ryden et al. European Heart Journal (2013) 34, 3035-3087

Impaired Glucose Tolerance Increases Mortality Risk: The DECODE Study



DECODE = Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe; n= 25364 men and women ≥ 30 years of Age.
OGTT = oral glucose tolerance test

DECODE Study Group. *Lancet*. 1999; 354:617–621

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Screening for Type 2 Diabetes & Prediabetes in Asymptomatic Individuals

- Type 2 diabetes testing
  - Adults of any age who are overweight or obese* and who have ≥1 diabetes risk factor
  - Begin testing at age 45
  - Normal test? Repeat at ≥3-year intervals
- Prediabetes testing
  - A1C, FPG, or 2-h PG after 75-g OGTT
  - Identify & treat other CVD risk factors
  - Consider testing in children and adolescents who are overweight or obese and have ≥2 diabetes risk factors

Diabetes Risk Factors
➢ Physical inactivity
➢ First-degree relative with diabetes†
➢ High-risk race/ethnicity
➢ Women who delivered a baby >9 lb or prior GDM diagnosis
➢ HDL-C <35 mg/dL ± TG >250 mg/dL
➢ A1C ≥5.7%, IGT, or IFG
➢ Hypertension (≥140/90 or on treatment)
➢ CVD history
➢ Conditions associated with insulin resistance‡

*Consider lower BMI cutoffs for Asian Americans
†African American, Latino, Native American, Asian American, Pacific Islander
‡Severe obesity, acanthosis nigricans, polycystic ovarian syndrome

ADA 2016 Guidelines

American Diabetes Association. *Diabetes Care*. 2016;39(suppl. 1):S1-S106.

Categories of Increased Risk for Type 2 Diabetes (Prediabetes)

FPG	2-hr PG*	A1C
100-125 mg/dL 5.6-6.9 mmol/L Impaired fasting glucose (IFG)	140-199 mg/dL 7.8-11.0 mmol/L Impaired glucose tolerance (IGT)	5.7-6.4% 39-46 mmol/mol

Risk is continuous, extending below lower limit of range and becoming disproportionately greater at higher ends of range

*In 75-g OGTT
FPG=fasting plasma glucose; OGTT=oral glucose tolerance test
PG=plasma glucose

ADA 2016 Guidelines

American Diabetes Association. *Diabetes Care*. 2016;39(suppl. 1):S1-S106.

Evidence-based classification used by ESC/EASD

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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Ryden et al. European Heart Journal(2013) 34, 3035-3087

Definition of pre-diabetes

Fasting glucose and 2-h blood glucose (OGGT)

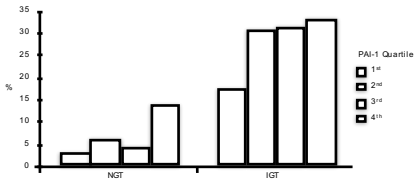
- Pre-diabetes definition (ADA)[1]
  - Impaired fasting glucose (IFG) 5.6–6.9 mmol/L
    or
  - Impaired glucose tolerance (IGT)
    2h glucose at OGGT 7.8–11.0 mmol/L
- Fasting glucose abruptly increases ~3yr and post OGTT ~5yr before the diagnosis of diabetes[2]
- Annual probability of developing diabetes
  - Both IGT and IFG: 10.8%[3]
  - IGT or IFR (not both) 5.4%[4]

[1]Genuth et al. *Diabetes Care*. 2003;26:3160–3167
[2]Tabak et al. *Lancet*. 2009;3732215–21
[3]Herman et al. *Ann Intern Med*. 2005;142:323-332
[4]De Vegt et al. *JAMA*. 2001;285:2109–2113

Outline

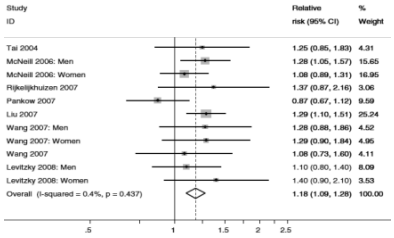
- Defining obesity, diabetes and pre-diabetes
- Obesity, fat distribution and insulin resistance
- Prevalence of obesity, diabetes and pre-diabetes
- Health risks to the person with pre-diabetes
- Benefits of weight loss

5 yr incidence of type 2 diabetes by quartiles of PAI-1 in subjects with normal (NGT) and impaired (IGT) glucose tolerance at baseline



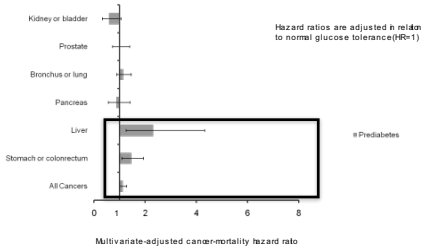
Festa et al. *Diabetes*. 200251:1131–1137

Association Between Impaired Fasting Glucose (100 to 125 mg/dl) and Cardiovascular Outcomes



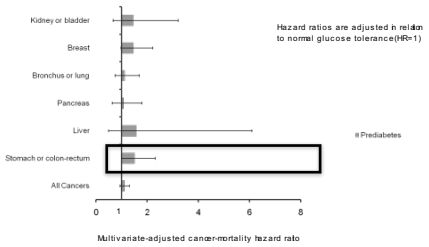
Ford et al. *JACC*. 2010;55:1310-17

Pre-diabetes and cancer mortality- men



Zhou et al. *Diabetologia*. 2010;531867-76

Pre-diabetes and cancer mortality- women



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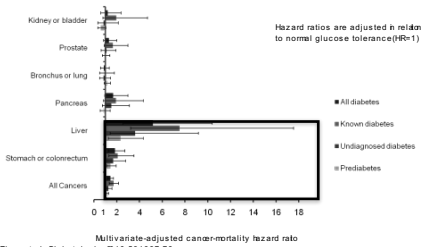
Pre-diabetes and cancer mortality- men



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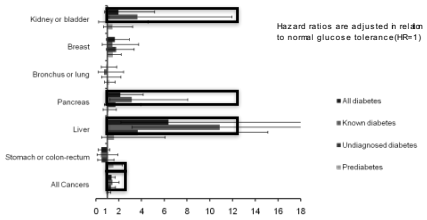

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- Pharmacological Interventions for prevention
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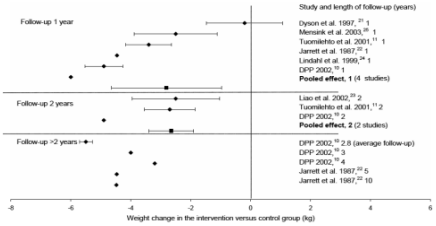
Effect of interventions on weight change in pre-diabetes



Norris et al. *Am J Prev Med*. 2005;28:126–139

Lifestyle intervention studies to lose weight and prevent type 2 diabetes

- Diabetes Prevention Program[1]
  - US, 3234 overweight men and women with IGT and IFG
  - diet plus exercise lifestyle intervention to lose weight vs. placebo and metformin vs. placebo (4-year follow-up)
- Diabetes Prevention Study (DPS)[2]
  - Finland, 522 overweight men and women with IGT
  - diet plus exercise lifestyle intervention to lose weight vs. placebo (6-year follow-up)
- Da Qing IGT and Diabetes Study (Da Qing)[3]
  - China, 530 men and women with IGT
  - diet, exercise, and diet plus exercise lifestyle interventions to lose weight vs. placebo (20-year follow-up)

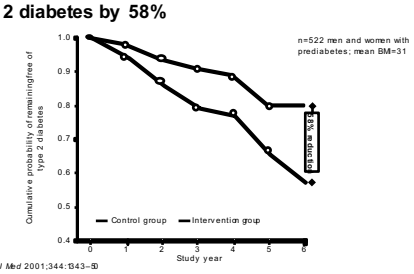
[1]Knowler et al. *N Engl J Med*. 2002;346:393–403; [2]Tuomilehtoet al. *N Engl J Med*. 2001;344:1343–50; [3]Pan et al. *Diabetes Care*. 1997;20:537–44

The Diabetes Prevention Study[1,2]

- 5 centres across Finland in men and women
  - Aged 40-65 years
  - BMI ≥25 kg/m^2
  - IGT: Defined as a 2-h plasma glucose 7.8-11.0 mmol/l following OGTT (75 g)
- 523 subjects were randomly assigned to either:
  - Lifestyle modification (n= 265)
  - Control (n=257)
- Interventions:
  - *Control*: initial general information on lifestyle changes and annual follow-up
  - *Intervention*: 7 sessions with a nutritionist during year 1 and a visit every 3 months thereafter aimed at reducing weight (target ≤25 kg/m^2), and dietary modification (<30% energy intake from fat). Individual guidance to increase physical activity.
- Mean subject disposition:
  - age, 55 years; BMI, 31.0 kg/m^2; gender, 67% female
- Average follow-up: 3.2 years

[1]Eriksson et al. Diabetologia. *199942*:793801; [2]TuomileHto et al *N Engl J Med*. 2001;3441343–50.

Diabetes Prevention Study showed that weight loss reduced risk of type 2 diabetes by 58%



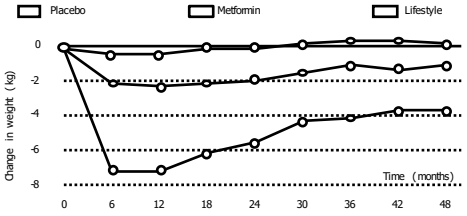
Tuomilehto et al. *N Engl J Med* 2001;344:1343–50

The Diabetes Prevention Program[1]

- 27 centres across the US in men and women
  - aged ≥25 years
  - BMI ≥24 (≥22 in Asians) kg/m²
  - ADA 1997 criteria for prediabetes[2]
- 3234 subjects were randomly assigned to either:
  - Intensive lifestyle modification (n= 1078)
  - Standard lifestyle recommendations plus metformin (850 mg BID) (n=1073)
  - Standard lifestyle recommendations plus placebo (BID) (n=1082)
- Lifestyle interventions:
  - *Intensive*: target ≥7% weight loss; ≥150 min weekly exercise; 16 lessons; individual and group sessions
  - *Standard*: written information; annual 30 min counselling
- Mean subject disposition:
  - age, 51 years; BMI, 34.0 kg/m²; gender, 68% female; race, 45% non-Caucasian
- Average follow-up (initial): 2.8 years

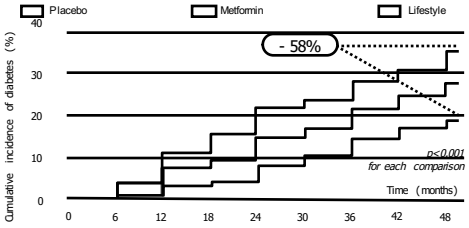
[1]Knowler et al. *N Engl J Med* 2002;346:393–403.

Diabetes Prevention Program: Effect of Interventions on Weight



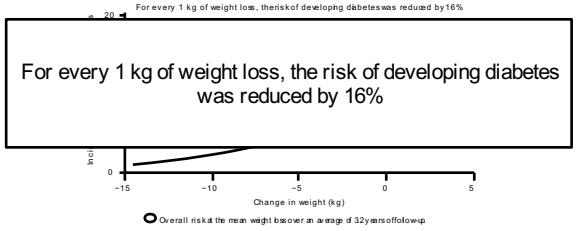
Knowler et al. *N Engl J Med*. 2002;346:393-403

Diabetes Prevention Program: Cumulative incidence of diabetes



Knowler et al. N Engl J Med. 2002;346:393-403.

Contribution of weight loss following lifestyle intervention to the risk of developing diabetes in DPP



Hamman et al. *Diabetes Care*. 2006;29:2102-7

Baseline factors predicting restoration of normal glucose regulation (NGR) in pre-diabetic subjects in the DPP

Predictors of regression to NGR	HR (95% CI)	P
ILS vs. placebo	2.05 (1.66–2.53)	0.0001
Metformin vs. placebo	1.25 (0.99–1.58)	0.0601
Younger age	1.07 (1.02–1.11)	0.0031
Male vs. female sex	1.17 (0.98–1.40)	0.0784
Caucasian vs. non-Caucasian	1.00 (0.84–1.19)	0.9986
Lower fasting plasma glucose	1.52 (1.36–1.68)	0.0001
Lower 2-h plasma glucose	1.24 (1.13–1.35)	0.0001
Greater insulin sensitivity (I/fasting insulin)	1.07 (0.99–1.16)	0.0934
Greater insulin secretion (CIR)	1.09 (1.01–1.17)	0.0353
Higher baseline weight	1.01 (0.92–1.11)	0.8229
Greater weight loss	1.34 (1.21–1.49)	0.0001

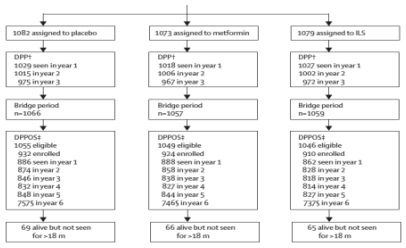
Perreault et al. *Diabetes Care*. 200932:1583-1588

The Diabetes Prevention Program Outcomes Study (DPPOS)

- Long-term follow-up of the Diabetes Prevention Program (DPP)
  - To investigate whether the delay in development of diabetes seen during the DPP can be sustained
  - To assess long-term effects of the interventions on health
    - diabetes incidence
    - weight change
    - cardiovascular
    - disease risk

DPP Research Group. Lancet ePub October 29, 2009 DOI:10.1016/S0140-6736(09)61457-4

The Diabetes Prevention Program Outcomes Study (DPPOS)



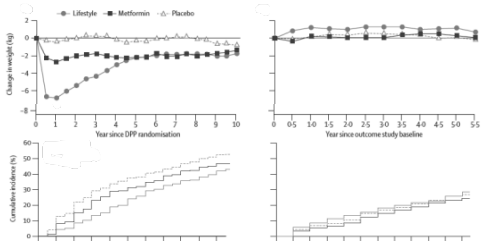
DPP Research Group. Lancet ePub October 29, 2009 DOI:10.1016/S0140-6736(09)61457-4

The Diabetes Prevention Program Outcomes Study (DPPOS)

- Participants informed of the main results from DPP
- Metformin and placebo groups entered into a 1–2 week drug washout study to identify whether treatment of fasting glucose accounted for the diabetes risk reduction with metformin
- Unmasked to their treatment assignments, and placebo stopped
- All participants, including the original lifestyle group and those who had developed diabetes, offered a group-administered version of the 16-session lifestyle curriculum as a bridge protocol
- DPPOS follow-up protocol was started in September, 2002
- Lifestyle sessions (HELP) were offered to all participants every 3 months
- Primary outcome, as in the DPP, was development of diabetes

DPP Research Group. Lancet ePub October 29, 2009 DOI:10.1016/S0140-6736(09)61457-4

Weight changes and diabetes incidence from Diabetes Prevention Program randomisation and enrolment in the DPPOS



DPP Research Group. Lancet ePub October 29, 2009 DOI:10.1016/S0140-6736(09)61457-4

Undiscounted, per capita, direct medical costs of care outside the DPP/DPPOS

Costs by year	Lifestyle	Metformin	Placebo
1-DPP	1,423	1,517	1,617
2-DPP	1,780	1,837	2,045
3-DPP	1,979	1,854	2,018
4 (Bridge)	2,059	2,087	2,330
5-DPPOS	2,015	2,174	2,543
6-DPPOS	2,519	2,493	2,636
7-DPPOS	2,645	3,061	2,875
8-DPPOS	3,444	3,607	3,319
9-DPPOS	3,291	3,298	3,265
10-DPPOS	3,406	3,686	4,822
Total	24,563	25,615	27,468
Costs by category			
Outpatient visits	6,845	7,145	7,325
Inpatient care	5,631	5,817	6,856
Emergency room visits	1,941	1,690	1,825
Urgent care visits	1,697	1,945	1,811
Calls to physicians	712	742	712
Prescription medications	6,490	6,619	6,959
Self-monitoring supplies and laboratory tests for diabetes	1,248	1,628	1,978
Total	24,563	25,615	27,468

DPP Research Group. Lancet ePub October 29, 2009 DOI:10.1016/S0140-6736(09)61457-4

Articles

The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study

Guangwei Li, Ping Zhang, Jinping Wang, Edward W Gregg, Wenying Yang, Qiuhong Gong, Hui Li, Hongliang Li, Yayun Jiang, Yali An, Ying Shuai, Bo Zhang, Jingling Zhang, Theodore J Thompson, Robert B Gerzoff, Gojka Roglic, Yinghua Hu, Peter H Bennett

Summary

Background Intensive lifestyle interventions can reduce the incidence of type 2 diabetes in people with impaired glucose tolerance.

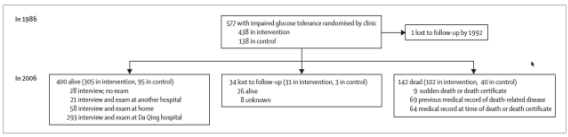
Lancet 2008; 371: 1783–89

The Da Quing Study – description and interventions[1,2]

- 33 centres across Da Quing, China; men and women
  - Aged ≥25 years
  - IGT: Defined as a 2-h plasma glucose 7.8-<11.1 mmol/l following OGTT (75 g)
- 577 subjects were randomly assigned to either:
  - age, 55 years; BMI, 31.0 kg/m²; gender, 46% female
  - Control (n=138)
  - Interventions; diet, exercise or both (n=438)
- Interventions:
  - *Control*: general info on diabetes and IGT; general brochures on diet & exercise but no individual sessions.
  - *Interventions:* Counselling sessions were conducted weekly for 1 month, monthly for 3 months, every 3 months thereafter
    - *Diet only*: for BMI >25 reduce calorieintake to achieve weightlosses of0.5-1.0kg per month until BMI=23. Dietary recommendations were individuallytaibred.
    - *Exercise only*: 1 exerciseunit ranged gentle (30mins) to very strenuous (5 mins). Age <50increase 2 unitsday, >50 1 unit/day.
    - *Diet & exercise*: Instructions and counselling similar to those described above
- Intervention and follow-up: 6 years and 20 years

[1]Pan et al. *Diabetes Care*. 1997;20:537–44; [2]Liet al.*Lancet*. 2008;371:1783–9.

The Da Quing Study – patient disposition



Li et al. Lancet 2008;371: 1783–89

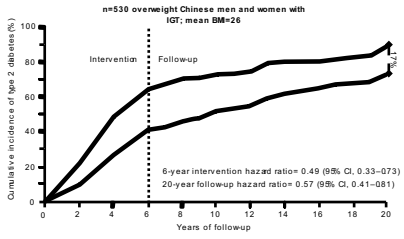
Da Qing study participants by group at baseline (1986), end of the 6-year active intervention (1992), and end of follow-up (2006)

	Control	Combined intervention
1986		
Total	(n=138)	(n=438)
Age (years)	46·6 (0·8)	44·7 (0·4)
Sex (men/women)	79/59	233/205
Body-mass index (kg/m²)	26·2 (0·3)	25·7 (0·2)
Fasting glucose (mmol/L)	5·52 (0·07)	5·60 (0·04)
2-h glucose level (mmol/L)	9·02 (0·08)	8·97 (0·02)
1992		
Total	(n=133)	(n=397)
Body-mass index (kg/m²)	25·8 (0·33)	25·2 (0·18)
2006		
Body-mass index (kg/m²)	(n=82) 24·4 (0·29)	(n=266) 24·5 (0·9)
Change in body-mass index from 1986 to 2006 (kg/m²)	(n=82) −1·57 (0·29)	(n=266) −1·41 (0·18)
Change in weight from 1986 to 2006 (kg)	(n=82) −4·2 (0·8)	(n=266) −3·7 (0·5)

Data are mean (SE). *p=0·0001, †p=0·05

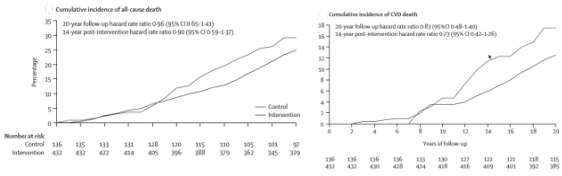
Li et al. Lancet 2008;371: 1783–89

Da Qing study, intervention and incidence of type 2 diabetes



Li et al. *Lancet*. 2008371:1783–9

Cumulative incidence of all-cause and cardiovascular mortality during follow-up in Da Qing Diabetes Prevention Outcome Study



Li et al. *Lancet*. 2008371:1783–9

Findings of four lifestyle intervention studies that aimed at preventing type 2 diabetes in subjects with impaired glucose tolerance

Study	Cohort size	Mean BMI (kg/m²)	Duration (years)	RRR (%)	ARR (%)	NNT
Malmö	217	26.6	5	63	18	28
DPS	523	31.0	3	58	12	22
DPP	2161[a]	34.0	3	58	15	21
Da Qing	500	25.8	6	46	27	25

RRR = relative risk reduction; ARR = absolute risk reduction/1000 person-years; NNT = numbers needed to treat to prevent one case of diabetes over 12 months.

[a]Combined numbers for placebo and diet and exercise groups.

From Ryden et al. *European Heart Journal*. 2007;28:88–136

Baseline factors predicting restoration of normal glucose regulation (NGR) in pre-diabetic subjects in the Diabetes Prevention Program

	HR (95% CI)	P
Regression to NGR		
ILS versus placebo	2.05 (1.66–2.53)	<0.0001
Metformin versus placebo	1.25 (0.99–1.58)	0.0601
Younger age	1.07 (1.02–1.11)	0.0031
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Perreault et al. *Diabetes Care*. 200932:1583-1588

UCL

Outline

- Case history
- For and against screening for diabetes and diagnosing prediabetes
- Definitions and prevalence
- Risks of impaired glucose metabolism
- Guidelines for screening and diagnostic criteria
- Lifestyle interventions for prevention
- Pharmacological Interventions for prevention
- Case History

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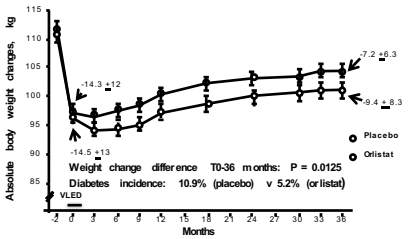
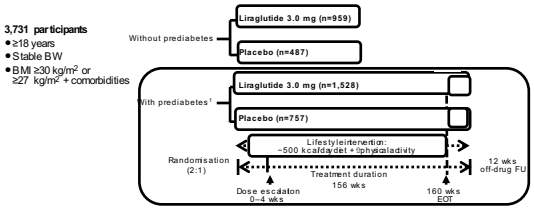
XENDOS trial (orlistat + very low calorie diet): Weight loss and diabetes incidence



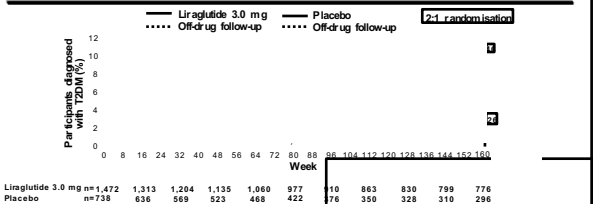
Richelsen et al. *Diabetes Care*. 2007;30:27–32

Trial design: SCALE Obesity and Prediabetes
Liraglutide 3.0 mg in weight management (160 weeks)



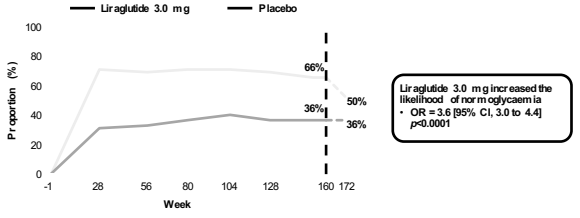
BW, body weight; EOT, end of treatment; FU, follow-up; HRQoL, health-related quality of life; wks, weeks
le Roux CW et al. Obesity Week; 2-6 November 2015; Los Angeles, CA, USA (T-PLB3843).
1. ADA. Diabetes Care 2010;33(Suppl. 1):S11-61

Proportion of subjects diagnosed with T2DM over time
0–172 weeks



Full analysis set. The figures show the cumulative probability of a diagnosis of T2DM over time that takes account of censoring to account. Numbers in the figure correspond to the accumulated number of diagnosed subjects T2DM diagnoses according to ADA 2010 criteria
ADA, American Diabetes Association; T2DM, type 2 diabetes mellitus
le Roux CW et al. Obesity Week 2015; 2-6 November 2015; Poster T-PLB3843

Regression to normoglycaemia
Measured at OGTT visits: 0–172 weeks



Full analysis set. Statistical analysis is logistic regression. CI, confidence interval; NNT, number needed to treat; OGTT, oral glucose tolerance test; OR, odds ratio
Fujioka et al. ENDO 2016; 1–4 April 2016, Abstract 2-465

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Outline

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- Pharmacological Interventions for prevention
- Case History

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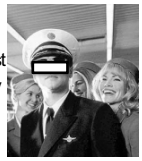
Case History

- JG is a 54 yr. old Caucasian commercial airline pilot
- He has passed his airline certification 6 months' ago
- He falls and sustains a Colles' fracture of his left wrist
- On admission to the fracture clinic, he has a capillary blood glucose measured
- The result is 5.7 mmol/l (104 mg) and he is told that he should see his doctor as he has pre-diabetes
- His father and brother both developed type 2 diabetes in their 70's
- He has a BMI of 30 kg.m^{-2}



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Case History

- Do you agree that he has pre-diabetes?

UCL

Case History

- Do you agree that he has pre-diabetes?
- Yes

Diagnosis	Venous plasma [a] mmol/L (mg/dL)	Venous blood mmol/L (mg/dL)	Capillary blood mmol/L (mg/dL)
IFG–FG	6.1 (110)	5.0 (90)	5.6 (101)
IGT–2hG	7.8 (140)	6.5 (117)	7.2 (130)
Diabetes–FG	7.0 (126)	5.8 (104)	6.5 (117)
Diabetes–2hG	11.1 (200)	9.4 (169)	10.3 (185)

- But this was taken under conditions of stress, so probably not valid

UCL

Case History

- If he does will this stop him flying?

UCL

Federal Aviation Administration

Aircraft Airports Air Traffic Data & Research Licen

Guide for Aviation Medical Examiners

CACI - Pre-Diabetes Worksheet (Updated 05/25/2016)
(Metabolic Syndrome, Impaired Fasting Glucose, Insulin Resistance, Glucose Elevation/Intolerance, Polycystic Ovary Syndrome)

The Examiner must review a current status report by the treating physician and any supporting documents to determine the applicant's eligibility for certification. If the applicant **meets ALL the acceptable certification criteria** listed below, the Examiner can issue. Applicants for first- or second- class must provide this information annually; applicants for third-class must provide the information with each required exam.

AME MUST REVIEW	ACCEPTABLE CERTIFICATION CRITERIA
Treating physician finds the condition stable on current regimen and no changes recommended	[ ] Yes
Symptoms associated with diabetes	[ ] None
Hypoglycemic events (symptoms or glucose less than or equal to 70 mg/dl) within the past 12 months.	[ ] None
Fasting blood sugar	[ ] Less than 126 mg/dl
Current A1C	[ ] Within last 90 days [ ]Less than or equal to 6.5 mg/dL
Oral glucose tolerance test, if performed	[ ] Less than 200 mg/dl at 2 hours [ ] N/A
Medications for condition	[ ] None [ ] Metformin only ((after a 14-day trial period with no side effects)

https://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item48/amd/diabetes/

UCL

Case History

- Are there further tests that you would want to do?
- Yes:
  - OGTT
  - HbA1c

Case History

- If these confirm a diagnosis of pre-diabetes would you treat him with
  - Advice on diet and exercise
  - Metformin
  - Other hypoglycaemic medication
  - Weight loss medication
- Lets discuss!!

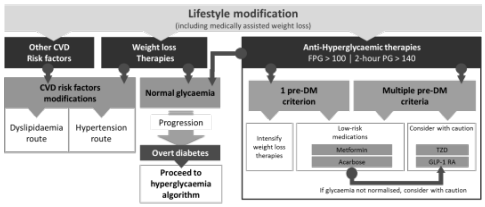
What to discuss with patients with pre-diabetes

- A diagnosis of pre-diabetes does not mean that you will develop diabetes. In fact, of 100 people like you, fewer than 50 are likely to develop diabetes in the next 10 years
- There are ways of reducing your risk of developing diabetes that involve changing your diet and being active. These can result from efforts you make as well as changes in your environment (food supply, workplace conditions, education, and other social determinants of health)
- There are drugs to delay diabetes, but these are the same drugs you will need if you do develop diabetes, and the value of starting them before you have developed diabetes is unknown

Yudkin and Montori. BMJ. 2014; 349: g4485

AACE prediabetes algorithm 2015

IFG (100–125 mg/dL) IGT (140–199 mg/dL) metabolic syndrome (NCEP 2005)



AACE, American Association of Clinical Endocrinologists and American College of Endocrinology; CVD, cardiovascular disease; DM, diabetes mellitus; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NCEP, National Cholesterol Education Program; PG, plasma glucose; TZD, thiazolidinedione

Garber AJ *et al. Endocr Pract* 2015;21:438–47.

Recommendations for Preventing or Delaying Type 2 Diabetes

Individuals with prediabetes: IGT, IFG, or A1C 5.7%-6.4%	Refer to intensive diet & physical activity behavior counseling program targeting •Weight loss (7% of body weight) •Increased physical activity (≥150 min/week moderate activity)
Consider metformin therapy for type 2 diabetes prevention in individuals with prediabetes	Especially in presence of •BMI >35 kg/m^2 •Age <60 years •Women with prior GDM

At least annual monitoring of individuals with prediabetes

Screen for and treat modifiable CVD risk factors: obesity, hypertension, dyslipidemia

DSME & DSMS appropriate for prediabetes to receive education and support for diabetes prevention or delay

Metformin is not FDA approved in the United States for type 2 diabetes prevention

CVD=cardiovascular disease; GDM=gestational diabetes mellitus; IFG=impaired fasting glucose; IGT=impaired glucose tolerance

ADA 2016 Guidelines

American Diabetes Association. *Diabetes Care* 2016;39(suppl 1):S1–S106