New Guidelines for the Diagnosis of Diabetes Mellitus

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Overview:

- Background and statistics
- Guidelines for diagnosis of DM
- Laboratory measurements
  - Hemoglobin A_{1c}
  - Standardization and Controversy
- Guidelines for prediabetes
- Guidelines for gestational DM

Diabetes Mellitus: Background and Statistics

Etiologic Classification: Diabetes Mellitus

Type 1 DM: 5-10%

- β-cell destruction
  - Immune-mediated (most)
  - Idiopathic (few)
- Acute presentation: polyuria, polydipsia, rapid weight loss
- Insulin dependent
- "IDDM," "juvenile"

Type 2 DM: 90-95%

- Depressed insulin secretion and/or insulin resistance
- Minimal symptoms; highly correlated with obesity
- Not insulin dependent
- "NIDDM," "adult"

http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf

National Diabetes Fact Sheet, 2011

FAST FACTS ON DIABETES

Diabetes affects 25.8 million people
8.3% of the U.S. population

DIAGNOSED
18.8 million people

UNDIAGNOSED
7.0 million people

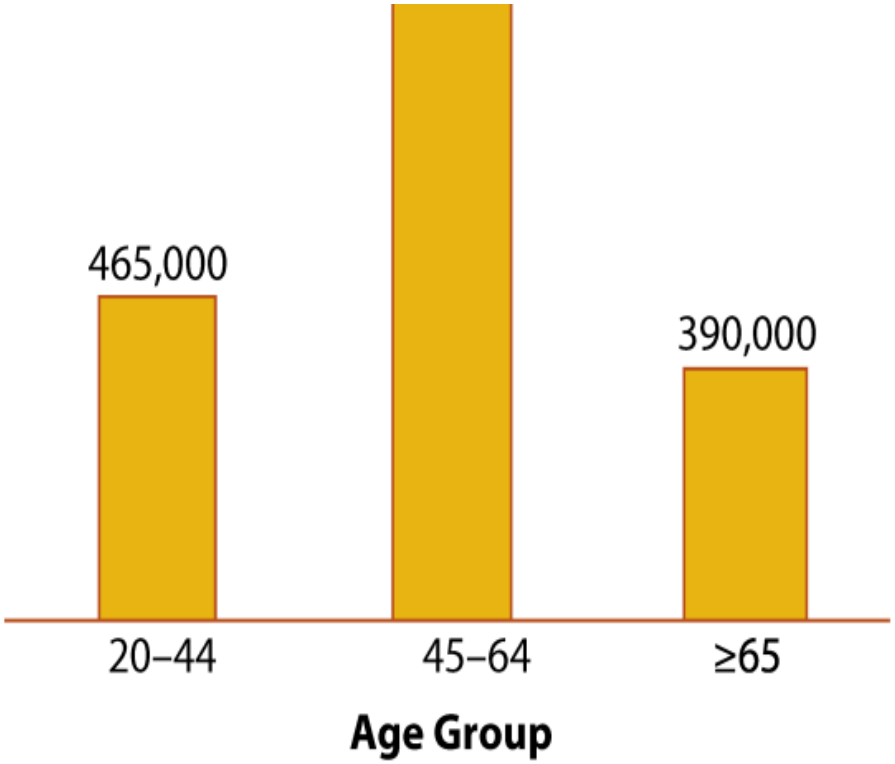
All ages, 2010

- 27% of diabetics are not diagnosed yet
- 79 million people are prediabetic (25%)

New cases of diagnosed diabetes

Estimated number of new cases of diagnosed diabetes among people aged 20 years or older, by age group, United States, 2010

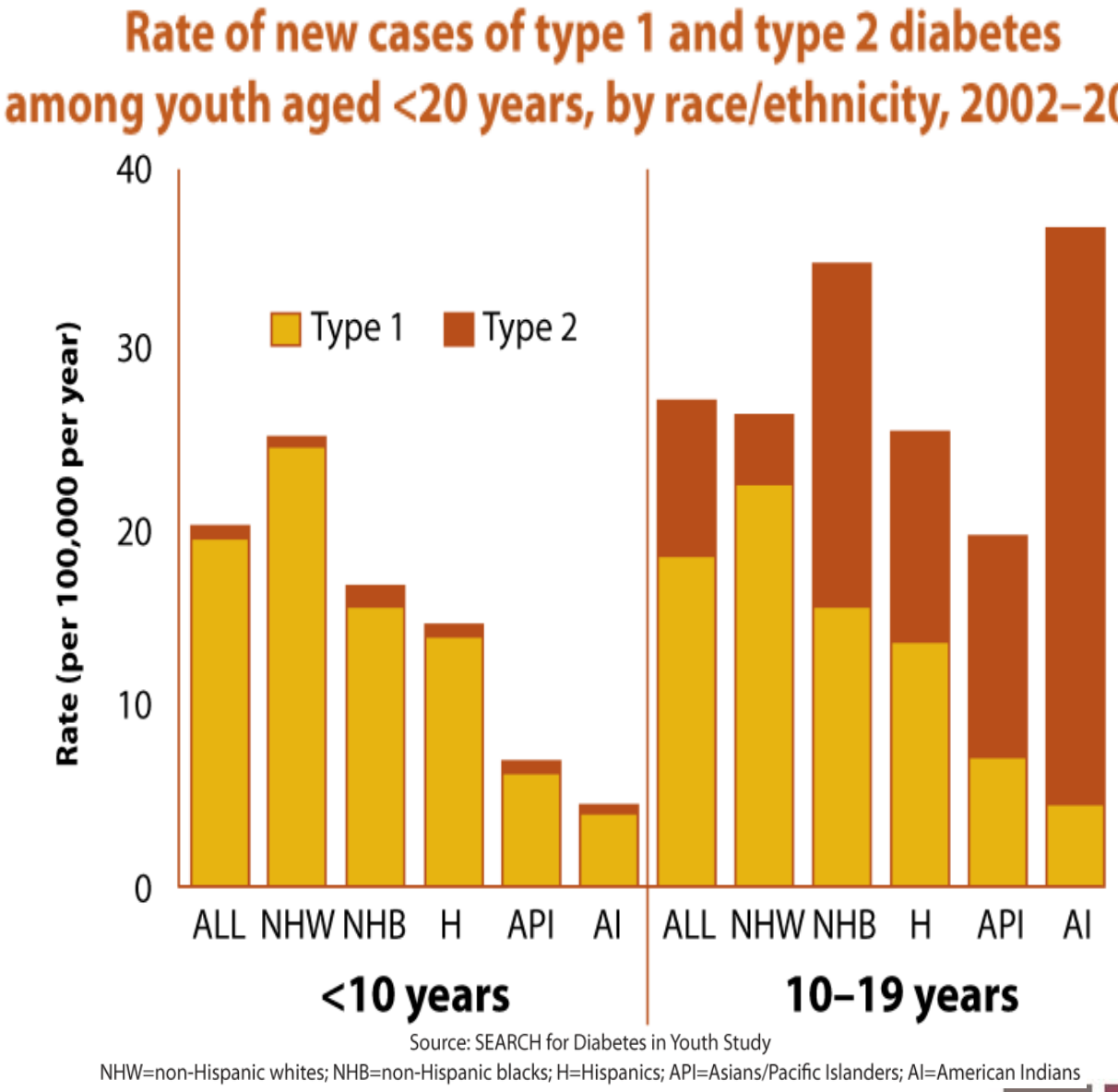
About 1.9 million people aged 20 years or older were newly diagnosed with diabetes in 2010.



Source: 2007–2009 National Health Interview Survey estimates projected to the year 2010

CDC National diabetes fact sheet. Atlanta, GA: 2011

New cases of diagnosed diabetes



CDC National diabetes fact sheet. Atlanta, GA: 2011

Diabetes Diagnosis: Children

- Type 2 DM increasing in younger populations
- Linked to obesity
- Projections (Diab Care 2012;35:2515)
  - 2001 to 2050
  - < 20 years of age
  - At current prevalence rates:
    - T2DM increases 49%
    - T1DM increases 23%
  - At increased prevalence rates (expected):
    - T2DM nearly quadruples
    - T1DM nearly triples
  - Greatest increase in racial/ethnic groups

Increasing Prevalence of Diagnosed Diabetes — United States and Puerto Rico, 1995–2010

MMWR / November 16, 2012 / Vol. 61 / No. 45

- Age-adjusted median prevalence of *diagnosed* diabetes increased from 4.5% to 8.2%
  - 1995: prevalence ≥ 6% in 3 areas*
  - 2010: prevalence ≥ 6% in ***all*** areas*
- Relative increase in prevalence ranged 9% - 227%
  - ≥ 50% increase in 42 states
  - ≥ 100% increase in 18 states
- Largest increases in Southern and Appalachian states
- In tandem with obesity
- Includes both T1 and T2

* All US states, DC, Puerto Rico

Increasing Prevalence of Diagnosed Diabetes — United States and Puerto Rico, 1995–2010

MMWR / November 16, 2012 / Vol. 61 / No. 45

- Why increased incidence of DM?
  - Improved survival of DM patients
    - Mortality in DM patients declined substantially 1997 – 2006
    - Faster decline than adults without DM
  - Improved diagnostics
  - Improved health, health care
- Why increases since 1995?
  - Demographic changes (increased elderly, minorities)
  - Increase in risk factors (obesity, sedentary lifestyle)
  - Changes in diagnostic criteria
  - Detecting previously undiagnosed DM

Diagnosis of DM: Guidelines

Table 4—*Criteria for testing for diabetes in asymptomatic adult individuals*

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2*) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250 mg/dl (2.82 mmol/l)
   - women with polycystic ovarian syndrome (PCOS)
   - A1C ≥5.7%, IGT, or IFG on previous testing
   - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - history of CVD
2. In the absence of the above criteria, testing for diabetes should begin at age 45 years.
3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

Table 5—*Testing for type 2 diabetes in asymptomatic children*

Criteria

- Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

Plus any two of the following risk factors:

- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS, or small-for-gestational-age birth weight)
- Maternal history of diabetes or GDM during the child's gestation

Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age

Frequency: every 3 years

American Diabetes Association

DIABETES CARE, VOLUME 34, SUPPLEMENT 1, JANUARY 2011

Updated DM Diagnosis Guidelines:

DIABETES CARE, VOLUME 32, SUPPLEMENT 1, JANUARY 2009

Table 2—*Criteria for the diagnosis of diabetes*

1. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*

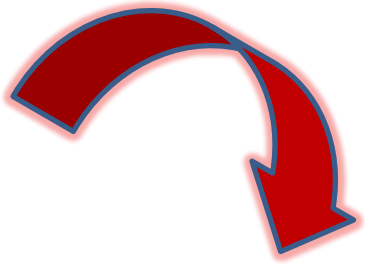
OR

2. Symptoms of hyperglycemia and a casual plasma glucose ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.

OR

3. 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.



ADA, AACE, EASD 2010

CDA, WHO, NACB 2011

DIABETES CARE, VOLUME 33, SUPPLEMENT 1, JANUARY 2010

Table 3—*Criteria for the diagnosis of diabetes*

1. A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*

OR

3. 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

What has changed?

Diabetes Care, volume 36, Supplement 1, January 2013

- Frequency of blood sugar testing for multi-dose insulin/pump therapies
  - Previously: SMBG “three or more times daily”
  - Now: SMBG “at least prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low BG, after treating low BG…, and prior to critical tasks such as driving.”
  - SMBG should be dictated by patient needs and treatment goals
- Assess CV risk factors in prediabetics
- Systolic blood pressure goal
  - Increased from 130 mm/Hg to 140 mm/Hg
  - Lower targets may be appropriate in some individuals

Diagnosis of DM: Laboratory Assays

Laboratory Assays Used in DM:

- Glucose
  - Random
  - Fasting
  - Oral glucose tolerance test
- Hemoglobin A_{1c}
  - Estimated average glucose
- Others
  - Fructosamine, glycated albumin
  - C-peptide, insulin
  - Microalbumin

Glycation of Hemoglobin: Background

- Glycated hemoglobin A: "HbA_1"
  - HbA_{1a}: fructose-1,6-diphosphate (HbA_{1a1}) or glucose-6-phosphate (HbA_{1a2}) at N-terminus of β chain
  - HbA_{1b}: pyruvate at N-terminus of β chain
  - HbA_{1c}: glucose at N-terminus of β chain **(>80% of HbA_1)**

Clinical Utility of HbA_{1c}:

- Red blood cell life-span is approximately 120 days
- Therefore, glycated hemoglobin reflects weighted average of plasma glucose concentration over the preceding 2-3 months
  - *What you ate that morning won't affect this test*
- HbA_{1c} tells you *how high* blood glucose is, and *how long* it has been elevated
- It is the only marker that correlates well with long term complications

Diabetes Control & Complications Trial (DCCT):

- Type 1 diabetic patients, no and mild retinopathy
- Two groups, 7 year avg study period, n = 1441
- HbA_{1c} measured by HPLC

Study Group	Mean Blood Glucose (mg/dL)	HbA1c (%)
Conventional	~ 240	~ 9
Intensive Treatment	~ 180	7.2
Non-diabetics	~ 100	< 6.1

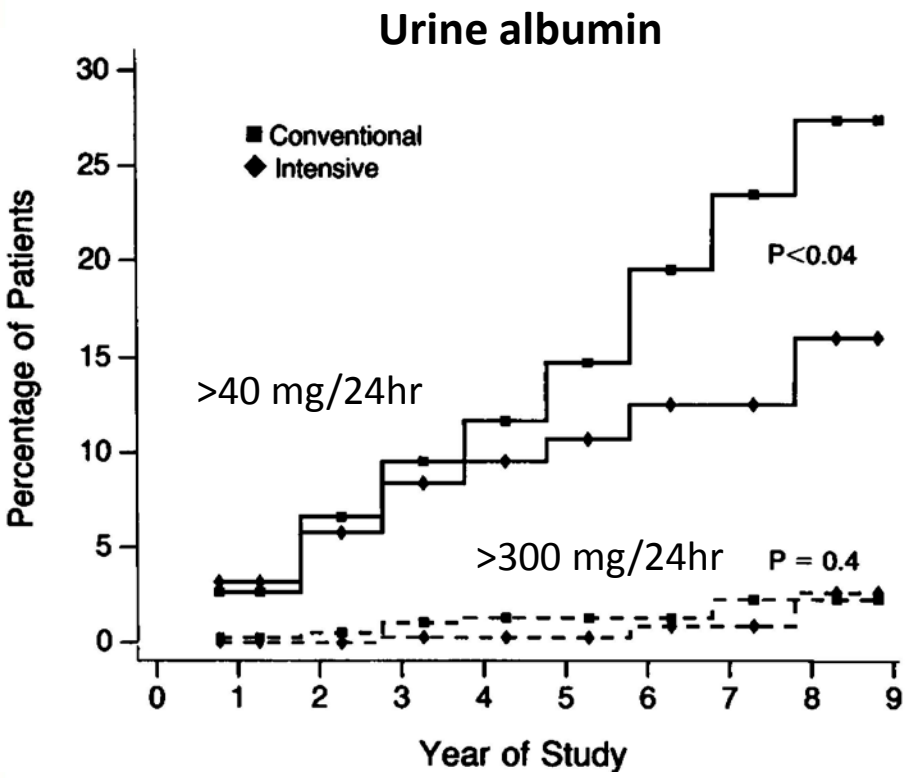
NEJM 1993;329:977

DCCT: Intensive Treatment Group

- 60% reduction in retinopathy, nephropathy, and neuropathy
- Threefold greater risk of hypoglycemia
- HbA_{1c} linked to retinopathy, cardiovascular disease
- Increased costs of intensive control offset by decreased complications and more productive lives
- *Unequivocally established value of HbA_{1c} measurements*

NEJM 1993;329:977

Intensive vs. Conventional Therapy:



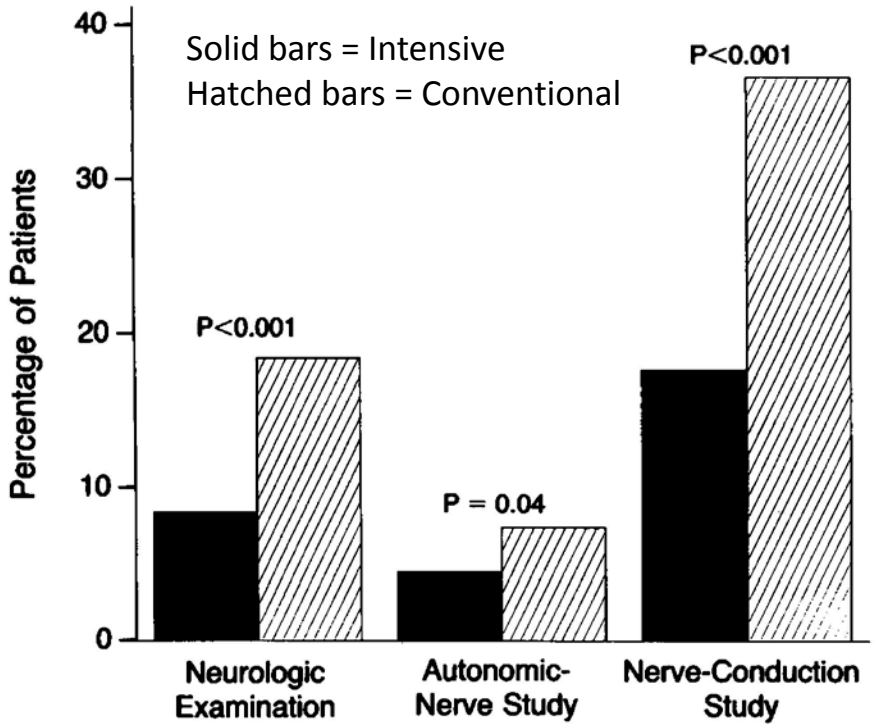
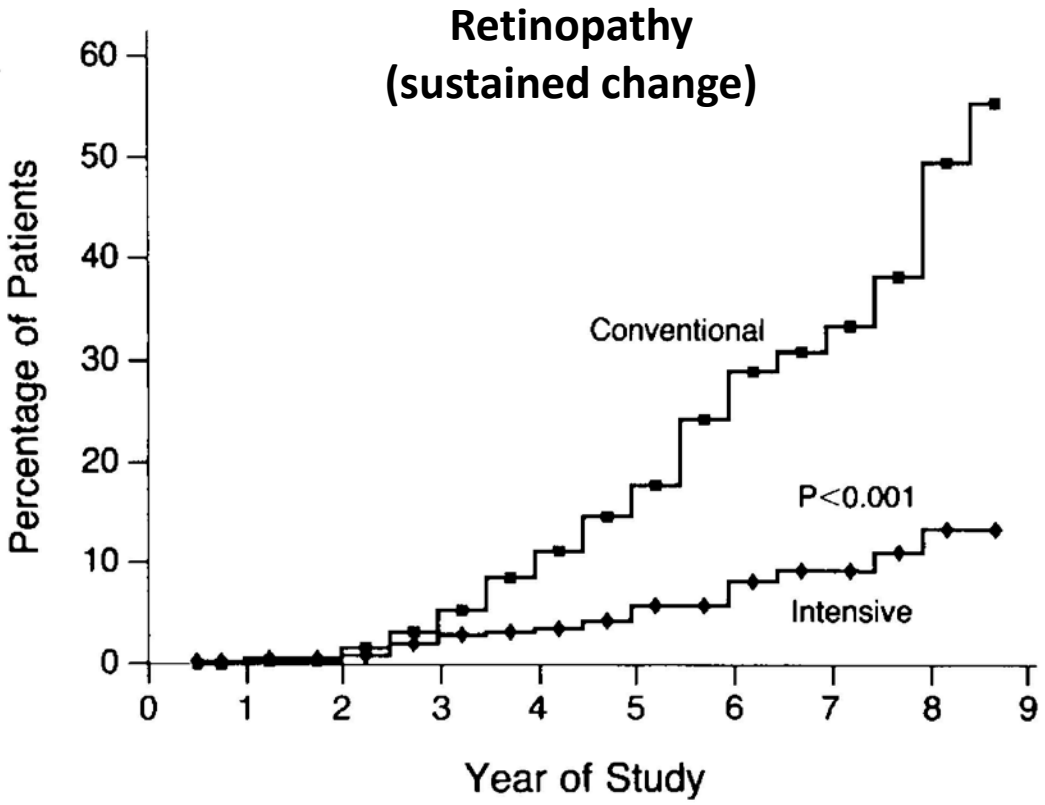


Figure 4. Prevalence of Abnormal Clinical Neurologic Examinations, Abnormal Results of Nerve-Conduction Studies, and Abnormal Autonomic-Nerve Studies at Five Years in Patients Receiving Intensive (Solid Bars) or Conventional (Hatched Bars) Therapy.

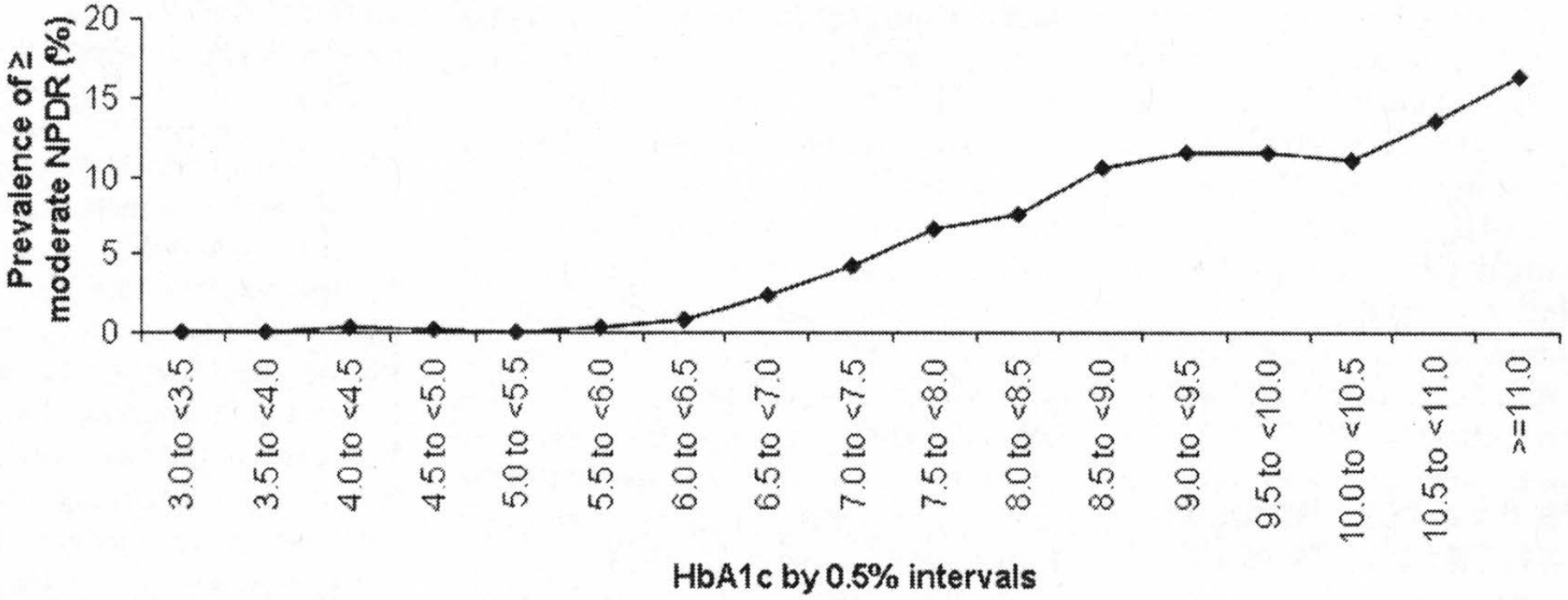
NEJM 1993;329:977

Intensive vs. Conventional Therapy:



NEJM 1993;329:977

Retinopathy and HbA_{1c}:



The International Expert Committee, Diabetes Care 2009;32:1327-34

United Kingdom Prospective Diabetes Study (UKPDS):

- Type 2 diabetic patients, followed 10 years, n = 3867
- HbA_{1c} method calibrated to DCCT HPLC method
- Conventional group HbA_{1c} = 7.9%; Intensive = 7.0%
- Link between HbA_{1c} and risk reduction
  - For every 1% decrease in HbA_{1c}:
    - Microvascular disease ↓ 37%
    - MI ↓ 14%
    - Death ↓ 21%

Lancet 1998;352:837; BMJ 2000;321:405

Conclusions from DCCT & UKPDS:

- *Small changes in HbA_{1c} related to reduced risk of complications in T1 and T2 DM*
- *HbA_{1c} measurements are useful*
- *Accurate, standardized HbA_{1c} test methods are required*

Diagnosis of DM: HbA_{1c} Standardization & Controversy

National Glycohemoglobin Standardization Program (NGSP): 1993

- Goal: certify results from individual methods are comparable to the HbA_{1c} method used in DCCT/UKPDS
- Central reference lab uses DCCT/UKPDS HPLC method; 8 secondary reference lab (commercial) methods calibrated to central result; those methods used to assist manufacturers
- Result: more labs report HbA1c, better accuracy, reduced variability

IFCC Standardization Effort: 1995

- International Federation of Clinical Chemistry and Laboratory Medicine
- Goal: Develop true reference method for HbA_{1c}
  - Rather than harmonizing to previous methods
  - Jeppsson et al., Clin Chem Lab Med 2002;40:78-89
- Separation with HPLC, quantitation with MS or CE
- Reference materials also produced

"mmol/mol"

NGSP vs. IFCC:

- Complementary roles:
  - IFCC establishes traceable methods
  - NGSP establishes limits of acceptable method performance
- Linear relationship between values
  - "Master equation" relates them
    - NGSP = 0.09148(IFCC) + 2.152
  - IFCC method 1.5-2% lower

NGSP vs. IFCC:

Table 4—*Comparison of HbA_{1c} values*

NGSP (%)	IFCC (mmol/mol)
4.0	20
5.0	31
6.0	42
6.5	48
7.0	53
8.0	64
9.0	75
10.0	86
11.0	97
12.0	108

NGSP values should be reported to one decimal; IFCC values should be without a decimal.

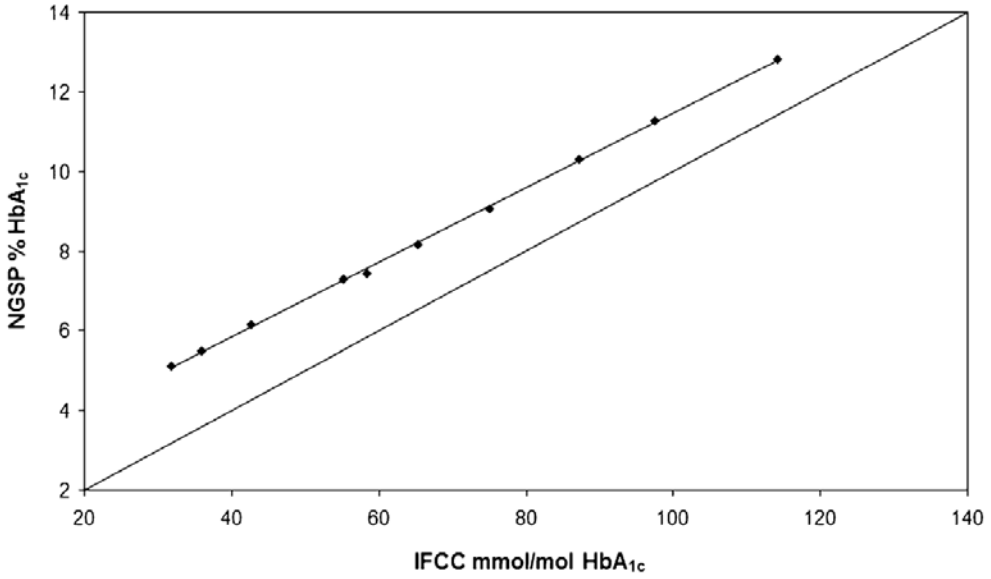


Figure 1—*Comparison of HbA_{1c} values between the NGSP and IFCC networks. HbA_{1c} was measured in 10 pooled blood samples by the NGSP (mean value of 7 network laboratories) and IFCC (mean value of 13 network laboratories) networks. ◆ is the regression line, and the solid black line is the y = x line (line of identity).*

Diabetes Care 2012;35:2674

NGSP vs. IFCC:

Table 5—*Units for reporting HbA_{1c} in selected countries*

Country	Original units†	Dual reporting initiated	Single reporting	
			Units	Date
Germany	NGSP	1 January 2009	SI	1 January 2010
Italy	NGSP	1 January 2011	SI	1 October 2011
The Netherlands	NGSP	1 January 2010	SI	1 January 2011
Sweden	Mono-S	1 September 2010	SI	1 January 2011
U.K.	NGSP	1 June 2009	SI	1 October 2011
Australia	NGSP	1 July 2011	SI	1 July 2013‡
New Zealand	NGSP	3 August 2009	SI	1 October 2011
Canada	NGSP	NA	NGSP	NA
Japan	JDS	1 April 2012	NGSP	1 April 2013‡
U.S.	NGSP	NA	NGSP	NA

JDS, Japan Diabetes Society; NA, not applicable. †All original units for reporting HbA_{1c} were %. ‡Anticipated date for conversion to single units.

Diabetes Care 2012;35:2674

Moving forward…

- Diabetes Care journal now requires both units:
  - % (NGSP)
  - mmol/mol (IFCC, SI)
- Rationale
  - Units are controversial
  - Compare past and future studies
  - Compare across countries
  - Global journal contributors

HbA_{1c} Controversy:

- Imperfect concordance between HbA_{1c} and FPG or 2hrPG:
  - "Glycation Gap"
  - NHANES: HbA_{1c} cutpoint of 6.5% identified 1/3 fewer cases of undiagnosed diabetes than FG cutpoint of 126 mg/dL
  - IRAS: HbA_{1c} detected fewer diabetics than OGTT, FPG, or these tests in combination (Lorenzo et al., Diab Care 2010;33:2104)
  - Patients with elevated HbA_{1c} and FPG were 32 times more likely to progress to diabetes than those with one test alone (Heianza et al., Lancet 2011;378:147)

HbA_{1c} Controversy:

- However…
  - Ease of use of HbA_{1c} promotes widespread application
  - May still increase number of diagnoses by sheer numbers, despite lower sensitivity

HbA_{1c}: Why now?

Been in use since early '90s for monitoring…
but not considered robust enough for *diagnosis*.

Problem #1:

- Standardization
  - NGSP standardization program (1993)
  - "Reference method" (HPLC used in DCCT) did not use pure HbA_{1c} for calibration

Resolution #1:

- IFCC-developed MS reference method
  - 1.5-2.0% lower than DCCT
  - IFCC calibrators recalculated to DCCT methods to eliminate bias (master equation)
  - "DCCT-aligned" calibrators

HbA_{1c}: Why now?

Problem #2:

- Inconsistent units
  - IFCC units are mmol/mol
    - "mmol of per mole of Hb"
  - Current HbA_{1c} reporting is %
  - Glucose reported mg/dL

Resolution #2:

- Linear relationship between HbA_{1c} and glucose methods established
  - Nathan et al., Diabetes Care 2008;31:1473-8
  - Report both HbA_{1c} (%) and eAG, which can be related to daily glucose levels (mg/dL)

HbA_{1c}: Why now?

Problem #3:

- Loose proficiency testing standards for HbA_{1c}

Resolution #3:

- CAP tightened variance requirements
  - 2007: ± 15% of target value
  - 2011: ± 7% of target value

Diagnosis of DM: PreDiabetes

Intermediate Diagnosis: Prediabetes

Table 3—*Categories of increased risk for diabetes (prediabetes)***

FPG 100–125 mg/dl (5.6–6.9 mmol/l): IFG

or

2-h plasma glucose in the 75-g OGTT 140–199 mg/dl (7.8–11.0 mmol/l): IGT

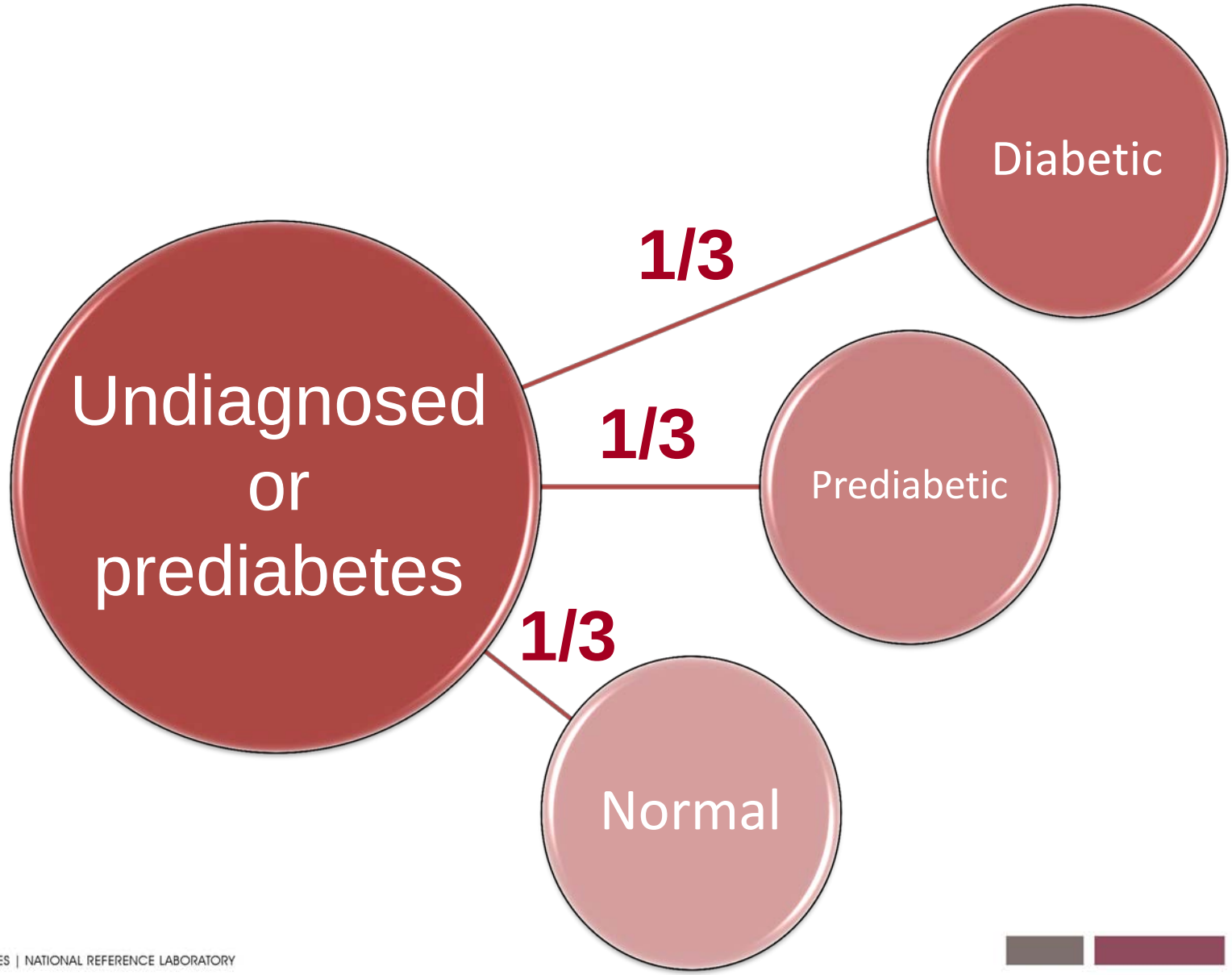
or

A1C 5.7–6.4%

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

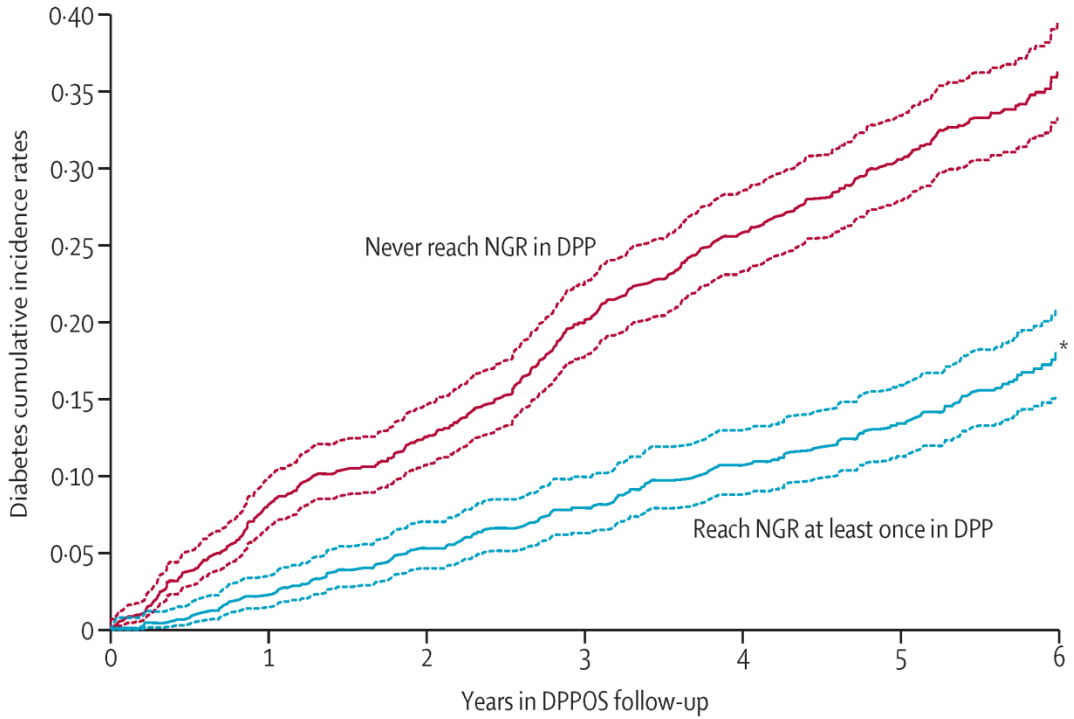
DIABETES CARE, VOLUME 34, SUPPLEMENT 1, JANUARY 2011

Prediabetes: Outcomes



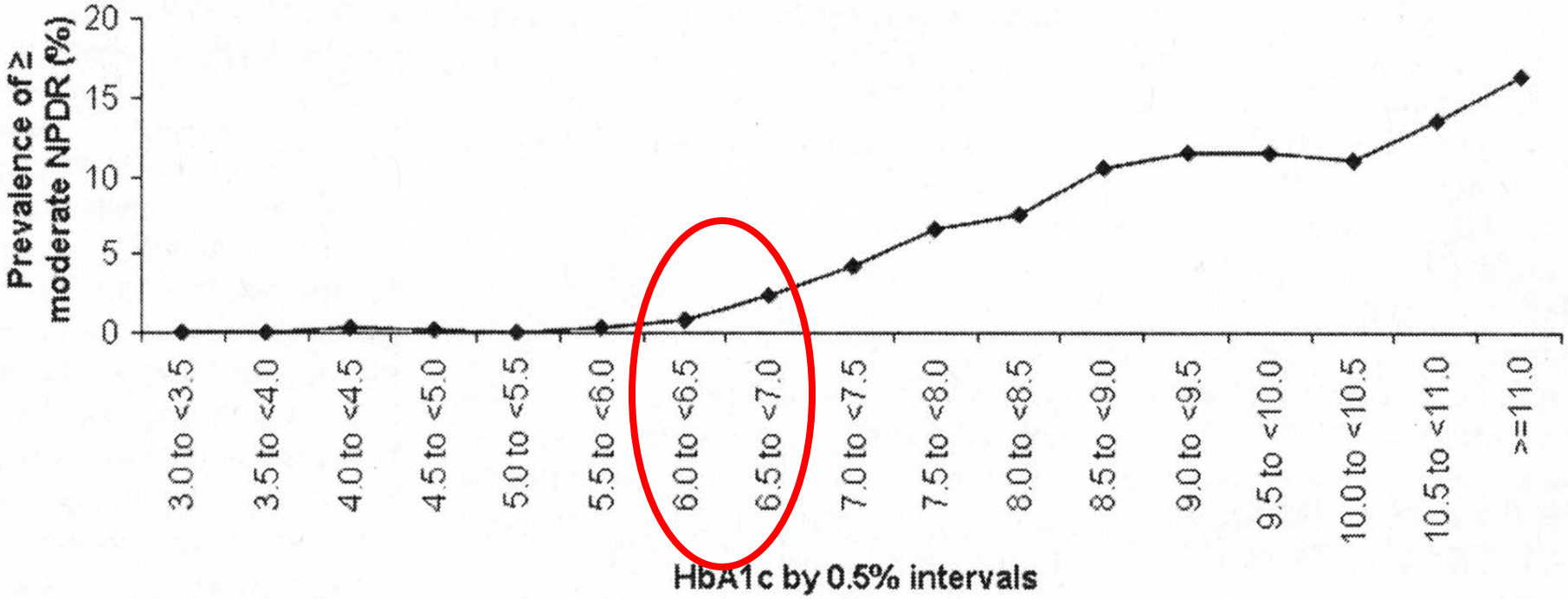
Prediabetes: Outcomes

- Outcomes from Diabetes Prevention Program (DPP)
- 3 groups
  - Lifestyle intervention, metformin, placebo
- Diabetes risk was 56% lower for those that returned to normal glucose regulation
  - Over 6 years
  - Lifestyle intervention OR medication
- Increased risk for stroke (21%), other complications
  - Lee et al., BMJ 2012;344:e3564



Perreault L et al., The Lancet 2012;379:2243

Retinopathy and HbA_{1c}:



The International Expert Committee, Diabetes Care 2009;32:1327-34

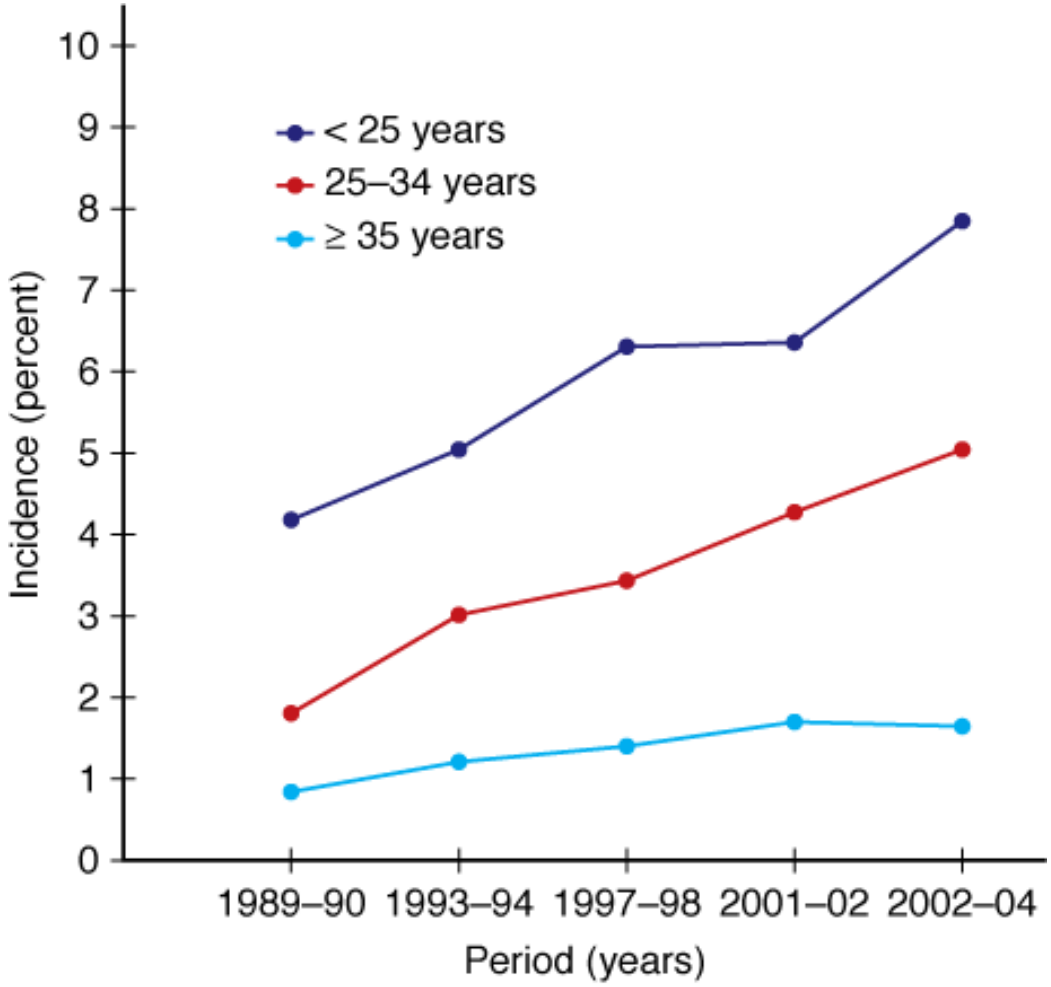
Diagnosis of DM: Gestational Diabetes Mellitus

Etiologic Classification: Diabetes Mellitus

Gestational DM: 1-14%

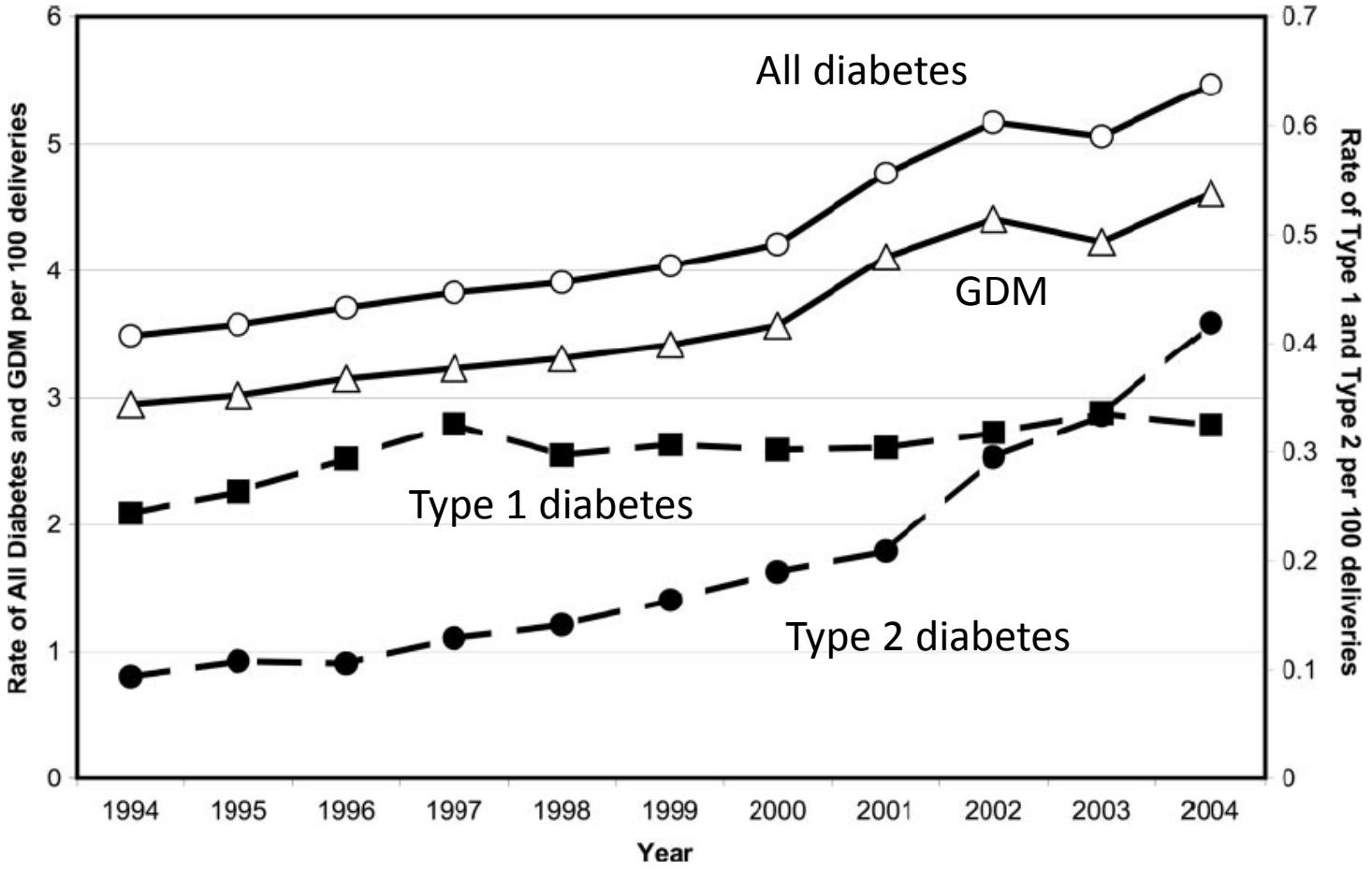
- Diabetes diagnosed during pregnancy
- Immediately after pregnancy: 5-10% of women with GDM are diagnosed with T2DM
- GDM = 35-60% chance of DM in next 10-20 years
- New criteria will classify increased numbers of GDM

U.S. GDM Trends:



AJOG 2008;198:525.e1-5

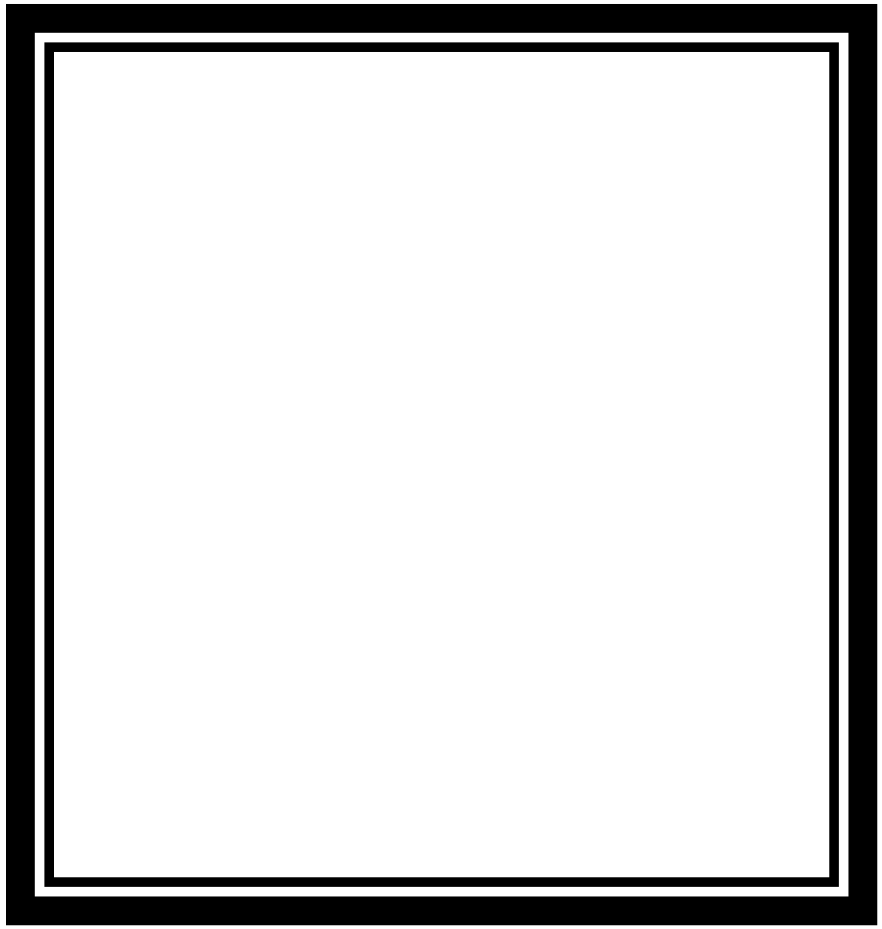
U.S. Diabetes Trends:



Diabetes Care 2010;33:768–773

Diagnosis: Gestational DM

- Woman has risk factors for T2DM?
  - Test at first prenatal visit
- No risk factors?
  Screen at 24-28 weeks
- Previously:
  - Low risk groups were not screened
  - Two tests required for diagnosis



DIABETES CARE, VOLUME 34, SUPPLEMENT 1, JANUARY 2011

Diagnosis GDM: Foundations

- Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study
  - NEJM 2008;358:1991
  - 25,000 pregnant women, 3rd trimester
  - Established relationship between maternal glycemia and adverse pregnancy outcomes
    - High birth weight
    - Cesarean section delivery
    - Neonatal hypoglycemia
    - Preeclampsia, preterm delivery, hyperbili
- International Association of Diabetes and Pregnancy Study Groups (IADPSG) put out criteria in 2010; ADA & NACB adopted 2011
  - WHO disagrees; ACOG guidelines differ (Obs&Gyn 2011;118:751)

ADA OGTT Guidelines:			
Patient Status	Glucose Load	Time Points	Cutoffs (mg/dL)
Fasting	75 g	Fasting 1 hour 2 hours	< 92 < 180 < 153

ACOG OGTT Guidelines:			
Patient Status	Glucose Load	Time Points	Cutoffs (mg/dL)
SCREEN: Fasting or Non-fasting	50 g	1 hour	< 130
DIAGNOSIS: Fasting	100 g	Fasting 1 hour 2 hour 3 hour	< 95 < 180 < 155 < 140

Adapted from: D. Stickle, NACBlog, 8/30/2011

Diagnosis GDM: Repercussions

- Significant increases in prevalence of GDM
  - Lower cutpoint
  - One result, not two
  - All women, not at-risk populations
- Numbers
  - Currently = 5-8% of pregnant women
  - ADA Guidelines = 17.8% of pregnant women (HAPO Study)
- ADA guidelines may take time to implement
  - Many clinicians follow ACOG guidelines

Summary Points:

- DM diagnosis and prevalence continues to increase
- HbA_{1c} values are considered diagnostic for DM
  - ADA, 2010
- HbA1c assays have been standardized (NGSP), but controversy over reporting units continues
- Diagnosis of the pre-diabetic state is important for long term outcomes
- Lack of consensus regarding GDM diagnostic criteria

Questions?

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