A Reappraisal of Prediabetes

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Prediabetes is diagnosed in individuals whose plasma glucose levels do not meet the criteria for diabetes but are too high to be considered normal (1). Such persons are considered to be at increased risk for the subsequent development of cardiovascular disease (CVD) and diabetes. Although the initiation of interventions and frequent follow-up are recommended, the presence of prediabetes is considered a risk factor rather than a clinical entity in its own right (1). Prediabetes is most often detected as a secondary consideration when a clinician performs one of the three recommended tests to diagnose diabetes. Hence, the diagnostic tests for diabetes/prediabetes include the measurement of glycated hemoglobin (HbA1c), fasting plasma glucose (FPG) or the 2-hour glucose concentration after a 75-g oral glucose tolerance test (OGTT).

Recent data suggest that prediabetes is present in 38% of US adults (2). Because so many individuals appear to be afflicted with prediabetes, it is important to examine the consequences of this risk state and consequently whether the future risks it portends are worthy of expending public or health plan resources at a time when health care expenditures are already considerable.

The history of prediabetes

In 1997, the American Diabetes Association (ADA) established the entity of impaired fasting glucose (IFG) as a prediabetes state defined as a FPG concentration of 110–125 mg/dL (6.1–6.9 mmol/L) (3). This criterion was adopted by the World Health Organization (WHO) (4). In 2003, the ADA lowered the criterion for IFG to 100–125 mg/dL (5.6–6.9 mmol/L) (5). This decision was based on the observation that many fewer persons with IFG subsequently developed diabetes than those whose prediabetes was diagnosed as impaired glucose tolerance (IGT) by a 2-hour glucose value on an OGTT of 140–199 mg/dL (7.8–11.0 mmol/L) (5, 6). Lowering the criterion for IFG to 100–125 mg/dL (5.6–6.9 mmol/L) enabled a similar number of people with IFG and IGT to subsequently develop diabetes, although different people might fall into the different diagnostic categories of prediabetes (5). The WHO did not adopt this new criterion for IFG (7).

In 2008, an Invited Expert Panel recommended that the diabetes community consider diagnosing diabetes with an HbA1c level of 6.5% or greater (48 mmol/mol), a value just under 3 SD above the National Health and Nutrition Examination Survey population mean. They also suggested that a HbA1c level of 6.0–6.4% (42–48 mmol/mol) (>2 SD above the population mean) mandated further testing and closer follow-up (8). The ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation then convened an International Expert Committee and agreed with the recommendation that, based on the association of diabetic retinopathy, diabetes could be diagnosed with a HbA1c level of 6.5% or greater (48 mmol/mol), if confirmed (9). They further argued that because of the continuum of risk in the subdiabetic glycemic range, dichotomous subdiabetic classifications (eg, prediabetes) are inappropriate and should not be created to define a specific at-risk group (9). Thus, they recommended that, given the lack of an identifiable threshold at which prevention efforts should be implemented, people with HbA1c levels of 6.0% or greater (42 mmol/mol), which is obviously near the diagnostic threshold, should be monitored more closely and should be considered candidates for an intervention to prevent diabetes (9).

The ADA formally accepted the recommendation for the diagnosis of diabetes but went further by adopting an HbA1c criterion for prediabetes of 5.7%–6.4% (39–48 mmol/mol) (1). The lower bounds of the HbA1c criterion

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Abbreviations: ADA, American Diabetes Association; CHD, coronary heart disease; CVD, cardiovascular disease; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization.

for prediabetes was apparently based on the cross-sectional values of the 2005–2006 National Health and Nutrition Examination Survey population that were fed into models that estimated the risk for developing diabetes and CVD (10), rather than on prospective studies. The WHO accepted the ADA recommendation on the HbA1c criterion for diagnosing diabetes but believed that that there was insufficient evidence to make any recommendations for values less than 6.5% (48 mmol/mol) (11).

As expected, using the ADA definition for prediabetes, the number of Americans potentially diagnosed with the condition is enormous, nearly 40% of the adult population (2). Gregg et al (12) have pointed out that the less strict the criteria used to identify prediabetes, the more people will be eligible for an intervention, and therefore, more individuals may be helped but at the cost of a large number for whom the intervention would not be necessary because they were not destined to develop diabetes. Conversely, the more strict the criteria for prediabetes, the fewer the individuals who will be eligible for an intervention, but there would be greater economic efficiency in that more cases of diabetes would be delayed per individual receiving the intervention.

Given the trade-offs identified by Gregg et al (12), the observation that achieving diabetes prevention in clinical trials (13–15) was expensive, and that sustainable weight loss has been very difficult to achieve in community settings (16, 17), all suggest that considerable resources would be necessary to prevent/delay the development of diabetes in a population. Moreover, and at the least before initiating nationwide programs, we should critically examine the evidence that prediabetes has clinical merit. Specifically, the question is whether an FPG of 100–109 mg/dL (5.6–6.0 mmol/L) or a HbA1c of 5.7–5.9 (39–41 mmol/mol) or even an FPG of 110–125

Table 1. Relationship Between Subdiabetic Hyperglycemia (Glucose Concentrations, FPG, mg/dL [mmol/L]) and Incident CVD

Reference	Population	Follow-Up, y	Outcomes	Results			
26	n = 2363 Dutch, aged 50–75 y	8	CVD death	Referent <94 (5.2) 94–99 (5.2–5.5), HR 0.82 100–109 (5.6–6.0), HR 0.52[a] 110–125 (6.1–6.9), HR 1.07			
27	n = 2789 Chinese, Malay, and Asian Indian males	8	Ischemic heart disease	100–109 (5.6–6.0), HR 1.13 110–125 (6.1–6.9), HR 1.51			
28	n = 36 386 Chinese aged >40 y	11	CVD death	100–109 (5.6–6.0), RR 1.00 110–125 (6.1–6.9), RR 1.51			
29	n = 2763 Postmenopausal US women with CHD	6.8	Nonfatal CHD	100–109 (5.6–6.0), HR 0.81 110–125 (6.1–6.9), HR 1.56[a]			
			CHD deaths	100–109 (5.6–6.0), HR 1.11 110–125 (6.1–6.9), HR 1.06			
			Any CHD event	100–109 (5.6–6.0), HR 0.90 110–125 (6.1–6.9), HR 1.37[a]			
			Stroke/TIA	100–109 (5.6–6.0), HR 1.30 110–125 (6.1–6.9), HR 1.35			
			Any CVD event	100–109 (5.6–6.0), HR 0.90 110–125 (6.1–6.9), HR 1.21			
30	Framingham Offspring n = 2163 women and 1895 men	15	4-y event rates			Women	Men
			CHD	100–109 (5.6–6.0)	OR	1.4	0.9
				110–125 (6.1–6.9)	OR	2.5[a]	0.9
			CVD	100–109 (5.6–6.0)	OR	1.1	1.1
				110–125 (6.1–6.9)	OR	2.1[a]	1.0
31	n = 384 795 Koreans aged >20 y	10	CVD	100–109 (5.6–6.0), HR 1.02 110–125 (6.1–6.9), HR 1.05[a]			
32	DECODE Study n = 29 714 aged 30–89 y	11	CVD death	Referent 81–109 (4.5–6.1) 110–125 (6.1–6.9), HR 1.6[a]			
33	n = 2651 Japanese >40 y old	7	CVD death	Referent <110 (6.1) 110–125 (6.1–6.9), HR 0.97			
34	DECODA Study n = 6817 Japanese and Asian Indian	5–10	CVD death	Referent <110 (6.1) 110–125 (6.1–6.9), HR 1.35			
35	ARIC Study n = 1328 aged 45–64 y	8–10	CHD event	Referent <94 (5.2) first quintile in people without diabetes 94 to <99 (5.2 to <5.5), RR 1.05 99 to <104 (5.5 to <5.8), RR 1.13 104 to <110 (5.8 to <6.1), RR 1.17 ≥110 (6.1), RR 1.06			

Abbreviations: ARIC, Atherosclerosis Risk in Communities; DECODA, Diagnostic Criteria in Asia; DECODE, Diagnostic Criteria in Europe; EPIC, European Prospective Investigation Into Cancer; HR, hazard ratio; n, number of persons followed up (either without diabetes at baseline if those numbers provided or entire population tested if not); OR, odds ratio; RR, relative risk; TIA, transient ischemic attack. Referent is less than 100 (5.6) unless otherwise stated.

[a] $P < .05$.

mg/dL (6.1–6.9 mmol/L) or a HbA1c of 6.0–6.4 (42–48 mmol/mol) represent sufficient risk of a clinical adverse outcome, ie, a CVD event or a microvascular complication, after prediabetes developed into diabetes, that would merit an intervention. (Since the OGTT is rarely used in nonpregnant individuals [18], we only evaluate the benefit of identifying those with prediabetes by the FPG or HbA1c criteria.)

The papers on which this Position Statement is based were identified in a comprehensive review of publications from 2003 through 2015. The ADA recommended the lower glucose bounds of prediabetes in 2003 and the lower HbA1c bounds of prediabetes in 2011. Only incident studies that separately tracked the association with CVD and the development of diabetes within the lower and upper bounds of the ADA definitions of prediabetes in the same population from 2003 were reviewed. This limited the number of studies analyzed in this manuscript because the vast majority related to this subject simply tracked subjects with IGT or individuals who fulfilled the entire definitions of the ADA or the WHO. Since 1995, the first author has published 20 papers on screening for and diagnosing diabetes and has kept an extensive file in this area. Articles in this file from 2003 through 2015 and their bibliographies were reviewed, and 31 papers that fulfilled the criteria mentioned above were identified and thus were included in this Position Statement.

Can we prevent CVD by treating prediabetes?

Although incident CVD will vary, depending on the intrinsic risk in the population being evaluated and the duration of follow up, comparisons within a study are valid. Among studies using incident CVD as the outcome, the evidence that the glycemia of prediabetes is an independent risk factor for CVD is not very strong. When risk factors for CVD were taken into account in persons with IFG, there was no increase in CVD with prediabetes diagnosed with either FPG concentrations of 110–125 mg/dL (6.1–6.9 mmol/L) (19, 20) or 100–125 mg/dL (5.6–6.9 mmol/L) (21–23). Similarly, in meta-analyses, adding FPG (24) or HbA1c (25) levels to the other risk factors did not improve the prediction for CVD.

We examined associations in different populations of various outcomes of incident CVD with preexisting glycemia, again with other risk factors for CVD taken into account. The associations as defined by FPG criterion are shown in Table 1. A cohort is defined as a separate defined population (eg, ethnic group, sex) in whom a specific CVD outcome (eg, coronary heart disease [CHD], stroke, CVD mortality, etc) was tracked. There was no increase in incident CVD with FPG concentrations of 100–109 mg/dL (5.6–6.0 mmol/L) in 13 cohorts compared with individuals with lower values. With FPG concentrations of 110–125 mg/dL (6.1–6.9 mmol/L), 11 cohorts showed no significant association, whereas six did (Figure 1).

Studies evaluating HbA1c levels compared values mostly of 5.5%–5.9% (37–41 mmol/mol) and those of 6.0%–6.4% (42–48 mmol/mol) with control values of less than 5.5% (37 mmol/mol) (Table 2). With HbA1C levels of 5.5%–5.9% (37–41 mmol/mol), there was no significant association in nine cohorts, whereas there was in three. With HbA1c levels of 6.0%–6.4% (42–48 mmol/mol), nine cohorts showed no significant association, whereas nine did (Figure 1).

Treating prediabetes to prevent diabetes

In contrast to the CVD outcomes of prediabetes, there is very good evidence that the glycemia of prediabetes is a risk factor for the development of diabetes. However, there is no threshold and the increased risk begins at FPG concentrations of 82–87 mg/dL (4.6–4.8 mmol/L) (43–45). The risk is curvilinear and increases faster the nearer the FPG concentration approaches 126 mg/dL (7.0 mmol/L), the criterion for diagnosing diabetes. As with incident CVD, the absolute incident rate of developing diabetes depends on the intrinsic risk of the population being examined, the duration of follow-up, but in this case, also the criteria used for the diagnosis of diabetes. Within each study though, a comparison of the lower bounds with the higher bounds of the criteria for prediabetes is valid.

There was a 4.6-fold increase (range 2.1–8.8) in the development of diabetes in individuals meeting the 110–

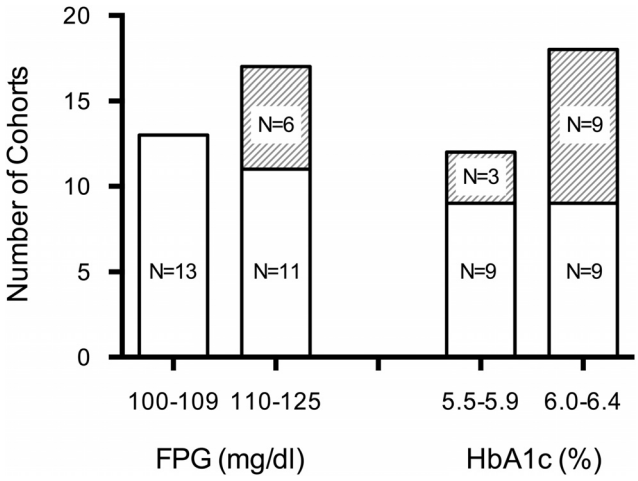

Figure 1. Predictive value of the lower and upper bounds of the criteria for prediabetes on incident CVD. A cohort is a separate defined population (eg, ethnic group, sex) in which a specific CVD outcome (eg, CHD, stroke, CVD mortality, etc) was tracked. Clear bar, association not statistically different from control group; striped bar, association statistically different from control group. Control groups had the following: FPG less than 100 mg/dL (5.6 mmol/L); HbA1c less than 5.5% (37 mmol/mol).

Table 2. Relationship Between Subdiabetic Hyperglycemia (HbA1c Levels, % [mmol/mol]) and Incident CVD

Reference	Population	Follow-Up, y	Outcomes	Results			
23	ARIC Study	14		Referent 5.0–5.4 (31–36)			
	n = 10 613; aged 45–64 y		CHD	<5.0 (<31), HR 0.96			
				5.5 to <6.0 (37 to <42), HR 1.23[a]			
				6.0 to <6.5 (42 to <48), HR 1.78[a]			
			Ischemic stroke	<5.0 (31), HR 1.09			
				5.5 to <6.0 (37 to <42), HR 1.17[a]			
				6.0 to <6.5 (42 to <48), HR 2.22[a]			
36	EPIC Study	6		Referent <5.0 (<31)			
	n = 4337 men and 5346					Women	Men
	women aged 45–79 y		CHD events	5.0–5.4 (31–36)	RR	0.96	1.56[a]
				5.5–5.9 (37–41)	RR	1.04	2.00[a]
				6.0–6.4 (42–48)	RR	2.29*	2.13[a]
			CVD events	5.0–5.4 (31–36)	RR	0.89	1.23
				5.6–5.9 (38–41)	RR	0.98	1.56[a]
				6.0–6.4 (42–48)	RR	1.63	1.79[a]
37	n = 3073 Japanese A-bomb survivors	8.8	CVD death	Referent <5.5 (<37)			
				5.5 to <6.0 (37 to <42), HR 0.99			
				6.0 to <6.5 (42 to <48), HR 1.63[a]			
38	Women's Health Study	10.1	CVD events	Referent <5.0 (31)			
	n = 26 443 aged >45 y			5.0–5.4 (31–36), RR 0.9			
				5.5–5.9 (37–41), RR 1.2			
				6.0–6.4 (42–48), RR 1.6			
39	n = 6406 Japanese	12.7		Referent <5.9 (41)			
	aged 30–79 y		CVD	6.0–6.4 (42–46), HR 1.2			
			CHD	6.0–6.4 (42–46), HR 0.8			
			Ischemic stroke	6.0–6.4 (42–46), HR 1.6			
40	n = 2213 Germans, majority had CHD	7.5	CVD death	Referent 5.5–5.9 (37–41)			
				<5.0 (31), HR 1.42			
				5.0–5.4 (31–36), HR 1.29			
				6.0–6.4 (42–46), HR 1.35			
41	n = 6803 Japanese	15		Referent <5.0 (31)			
	aged ≥30 y		CVD death	5.0–5.4 (31–36), HR 1.31			
				5.5–5.9 (37–41), HR 1.38			
				6.0–6.4 (42–46), HR 2.18[a]			
			CHD death	5.0–5.4 (31–36), HR 1.20			
				5.5–5.9 (37–41), HR 1.46			
				6.0–6.4 (42–46), HR 1.11			
			Stroke death	5.0–5.4 (31–36), HR 1.19			
				5.5–5.9 (37–41), HR 1.38			
				6.0–6.4 (42–46), HR 2.74[a]			
42	n = 1336 Europeans and 1139 South Asians	20	European	Referent <5.7 (39)			
			CHD	5.7–6.4 (39–46), HR 1.12			
				6.0–6.4 (42–46), HR 1.68[a]			
			Stroke	5.7–6.4 (39–46), HR 0.95			
				6.0–6.4 (42–46), HR 0.85			
			South Asian				
			CHD	5.7–6.4 (39–46), HR 0.98			
				6.0–6.4 (42–46), HR 1.00			
			Stroke	5.7–6.4 (39–46), HR 1.60			
				6.0–6.4 (42–46), HR 1.73[a]			

ARIC, Atherosclerosis Risk in Communities; EPIC, European Prospective Investigation Into Cancer; HR, hazard ratio; n, number of persons followed up (either without diabetes at baseline if those numbers provided or entire population tested if not).

[a] $P < .05$.

125 mg/dL (6.1–6.9 mmol/L) criterion compared with those whose FPG was 100–109 mg/dL (5.6–6.0 mmol/L) (Table 3 and Figure 2). Similarly, there was a 3.7-fold increase (range 2.0–6.5) in the development of diabetes in individuals with HbA1c levels of 6.0% or greater (42 mmol/mol) compared with those with HbA1c levels of 5.5%–6.0% (37–42 mmol/mol) (Table 4 and Figure 2).

Discussion

Although the evidence that prediabetes is an independent risk factor for CVD is weak, especially for FPG of 100–109 mg/dL (5.6–6.0 mmol/L) (Table 1) and HbA1c less than 6.0% (42 mmol/mol) (Table 2), there is strong evidence for a progressive curvilinear increasing risk of glycemia for the development of diabetes (Tables 3 and 4). At FPG levels of 110–125 mg/dL (6.1–6.9 mmol/L) or HbA1c levels of 6.0%–6.4% (42–48 mmol/mol), there is about a 4-fold increase in the risk of developing diabetes compared with lower FPG levels of 100–109 mg/dL (5.6–6.0 mmol/L) or HbA1c levels of 5.5–5.9% (37–41 mmol/mol).

In addition to lifestyle interventions for those diagnosed with prediabetes, based on the results of the Diabetes Prevention Program consideration of metformin therapy for obese individuals younger than 60 years of age has been suggested (59). When metformin was discontin-

Table 3. Effect of Subdiabetic Hyperglycemia (Glucose Concentrations, FPG, mg/dL [mmol/liter]) on Development of Diabetes

Reference	Population	Follow-Up, y	Outcome	Results		
27	n = 2789 Chinese, Malay and Asian Indian males	8	Developing diabetes/8 y, % Criteria: OGTT or Rx for diabetes	100–109 (5.6–6.0), 22.2 110–125 (6.1–6.9), 55.2		
30	Framingham Offspring n = 3634	4	Developing diabetes/4 y, % Criteria: FPG ≥126 (7.0) or Rx with OHA or insulin		Women	Men
				<100 (5.6)	0.3	0.6
				100–109 (5.6–6.0)	4.0	4.5
				110–125 (6.1–6.9)	27.8	20.0
46	Mayo Clinic n = 7408	9	Developing diabetes/9 y, % Criterion: FPG ≥126 (7.0)	<100 (5.6), 6.7 100–109 (5.6–6.0), 18.5 110–125 (6.1–6.9), 38.6		
47	Hoorn Study n = 1342 Dutch aged 50–75 y	6.4	Developing diabetes/6.4 y, % Criterion: OGTT	<100 (5.6), 5 100–109 (5.6–6.0), 14 110–125 (6.1–6.9), 44		
48	DESIR Study n = 2276 women and 2176 men aged 30–64 y	6	Incidence/1000 person-years Criteria: FPG ≥126 (7.0) or Rx with OHA		Women	Men
				<100 (5.6)	0.7	1.8
				100–109 (5.6–6.0)	6.2	5.7
				110–125 (6.1–6.9)	54.7	43.2
49	n = 5452	6.1	Developing diabetes/y, % Criteria: ICD-9 code, FPG ≥126 (7.0) or Rx with OHA or insulin	100–109 (5.6–6.0), 1.34 110–125 (6.1–6.9), 5.16		
50	n = 449 Japanese aged 23–65 y	5	Developing diabetes/y, % Criteria: FPG ≥126 (7.0) or clinically treated diabetic	<100 (5.6), 0.1 100–109 (5.6–6.0), 2.0 110–125 (6.1–6.9), 6.9 (independent of HbA1c levels)		
51	n = 6804 Japanese men aged 40–55 y	4	Developing diabetes/4 y, Criteria: FPG ≥126 (7.0) or Rx with OHA or insulin	<100 (5.6), 2.8 100–109 (5.6–6.0), 11.1 110–125 (6.1–6.9), 42.1		

DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome; ICD-9, *International Classification of Diseases*, ninth revision; n, number of persons followed up (either without diabetes at baseline if those numbers provided or entire population tested if not); OHA, oral hypoglycemic agent; Rx, treatment.

ued at the end of the study in the 668 subjects who did not have diabetes while on the drug, 48, or 7.2%, met the OGTT criteria for diabetes when tested within 1–2 weeks (60). Similarly, other drugs, such as acarbose (61), troglitazone (62), and rosiglitazone (63) have also been effective in delaying the development of diabetes in people with IGT. However, within a very short period of time after discontinuing these drugs, the incidence rates of developing diabetes were the same as the rates in those who had received the placebo. This strongly suggests that these drugs do not affect the intrinsic rate of glycemic rise in an individual but simply treat the prevailing glucose levels delaying the time that these individuals will cross the line to values that meet the diagnostic criteria of diabetes. Because initiation of drug therapy (usually metformin) is recommended when diabetes is diagnosed (64), does this not simply lower the diagnostic cut point of diabetes? Whether the diagnostic cut point should be lowered requires much public discussion and scientific justification, which has not to our knowledge occurred.

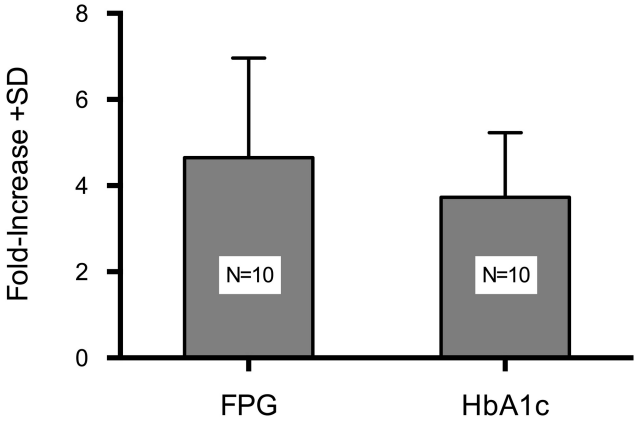

Figure 2. Relationship of the upper and lower bounds of the criteria for prediabetes on the development of diabetes. Fold increase was the risk of developing diabetes in individuals meeting the higher bounds (FPG, 110–125 mg/dL [6.1–6.9 mmol/mol]; HbA1c, 6.0%–6.4% [42–48 mmol/mol]) divided by the lower bounds (FPG, 100–109 mg/dL [5.6–6.0 mmol/L]; HbA1c, 5.5%–5.9% [37–41 mmol/mol]) of the criteria for diagnosing prediabetes.

Of note, even if no interventions are initiated in people with prediabetes or if diabetes develops despite them, HbA1c levels just above the threshold for diabetes (6.5% [48 mmol/mol] through 6.9% [52 mmol/mol]) may not be clinically deleterious. Two randomized control trials (65, 66) and three observational studies (67–69) have clearly demonstrated that if HbA1c levels are kept below 7.0% (53 mmol/mol) in diabetic patients, there is no development or progression of the microvascular complications of diabetes. Thus, from a clinical perspective, identifying asymptomatic people with an FPG between 110 and 125 mg/dL (6.1–6.9 mmol/L) or an HbA1c of 6.0%–6.4% (42–48 mmol/mol) is not at all too late to prevent diabetes-related complications, even if treatment (70) commenced only upon the diagnosis of diabetes.

Table 4. Effect of Subdiabetic Hyperglycemia (HbA1c Levels, % [mmol/mol]) on Development of Diabetes

Reference	Population	Follow-Up, y	Outcome	Results
23	ARIC Study n + 11 092	14	Developing diabetes/14 y, % Criteria: self-reported diagnosis or use of diabetic medications	Referent 5.0 to <5.5 (31–37) <5.0 (31), 0.5 5.5 to <6.0 (37–42), 2.44 6.0 to <6.5 (42–48), 9.20
38	Women's Health Study n = 26 443 aged >45 y	10.1	Incidence/1000 person-years Criterion: self-report	Referent <5.0 (31) 5.0–5.4 (31–36), RR 2.9 5.5–5.9 (37–41), RR 12.1 6.0–6.4 (42–46), RR 29.3
51	n = 6804 Japanese men aged 40–55 y	4	Developing diabetes/4 y Criteria: FPG ≥126 (7.0) or Rx with OHA or insulin	<5.4 (36), 3.0 5.4–5.7 (36–39), 6.5 5.8–6.2 (40–44), 20.6 6.3–6.7 (45–50), 41.9
52	n = 1197 veterans	3	Developing diabetes/y, % Criteria: self-report, FPG ≥126 (7.0) or HbA1c ≥7.0 (53)	4.6–5.0 (27–31), 0.67 5.1–5.5 (32–37), 0.90 5.6–6.0 (38–42), 2.53 6.1–6.5 (43–48), 6.41
53	DESIR Study n = 2820 aged 30–65 y	6	Incidence of diabetes at 6 y Criteria: FPG ≥126 (7.0) or Rx with OHA or insulin	Referent <4.5 (26) 4.5–5.0 (26–31), OR 0.9 4.5–5.5 (26–37), OR 1.5 4.5–6.0 (26–42), OR 5.0 4.5–6.5 (26–48), OR 32.7
54	n = 12 375 veterans	8	Risk of developing diabetes Criteria: ICD-9 code or Rx for diabetes	Referent <4.5 (26) 4.5–4.9 (26–30), OR 1.01 5.0–5.4 (31–36), OR 1.70 5.5–5.9 (37–41), OR 4.87 6.0–6.5 (42–48), OR 16.06
55	n = 1791 Koreans	4	Developing diabetes/4 y, % Criteria: FPG ≥126 (7.0) or HbA1c ≥6.5% (48)	5.7–5.9 (39–41), 13.3 6.0–6.4 (42–46), 45.4
56	EPIC Study n = 5735	3	Risk of developing diabetes Criteria: self-report, Rx with diabetes medication or HbA1c ≥6.5% (48)	Referent <5.0 (31) 5.0–5.4 (31–36), OR 1.6 5.5–5.9 (37–41), OR 3.3 6.0–6.4 (42–46), OR 15.6
57	n = 842 aged 40–79 y	15	Risk of developing diabetes Criteria: ongoing diabetes Rx or HbA1c ≥6.5% (48)	Referent 5.00–5.49 (31–36) 5.50–5.99 (37–42), HR 3.21 6.00–6.49 (42–48), HR 9.26
58	DPP n = 932 placebo subjects	3.2	Subjects developing diabetes/100 person-years Criterion: HbA1c ≥6.5% (48)	<5.5 (37), 0.4 5.5–5.9 (37–41), 3.6 6.0–6.4 (42–46), 21.0

ARIC, Atherosclerosis Risk in Communities; DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome; DPP, Diabetes Prevention Program; EPIC, European Prospective Investigation Into Cancer; HR, hazard ratio; ICD-9, *International Classification of Diseases*, ninth revision; n, number of persons followed up (either without diabetes at baseline if those numbers provided or entire population tested if not); OHA, oral hypoglycemic agent; OR, odds ratio; RR, relative risk; Rx, treatment.

Recommendations

Given the weakness of the evidence that the glycemia of prediabetes is a risk factor for incident CVD, especially in those diagnosed by the lower ADA bound criteria, and the 4-fold increased risk of developing diabetes in people meeting the upper bounds of the ADA's criteria for the diagnosis of prediabetes compared with the lower bound, we strongly recommend defining prediabetes as FPG levels of 110–125 mg/dL (6.1–6.9 mmol/L) or HbA1c levels of 6.0%–6.4% (42–48 mmol/mol), the criteria suggested by the WHO, the Invited Expert Panel, and the International Expert Committee.

Given that prediabetes does not appear to be a significant risk factor for CVD and there is a much lower risk of developing diabetes at FPG levels of 100–109 mg/dL (5.6–6.0 mmol/L) or HbA1c levels of 5.5%–5.9% (37–41 mmol/mol), we recommend that scarce public and health plan resources available for the prevention of diabetes be directed only toward people with a FPG of 110–125 mg/dL (6.1–6.9 mmol/L) or an HbA1c of 6.0%–6.4% (42–48 mmol/mol). In this time in which the cost of health care continues to rise, occupies a major portion of America's gross domestic product, and there is intense competition for funds to combat already established acute and chronic diseases, lifestyle interventions should be provided (via government or health plan funded programs) only to those closer to the diagnostic criteria for diabetes. As has been said, economic efficiency (12) dictates that interventions are warranted when there is the greatest chance of delaying the development of diabetes.

Finally, individuals who have mild hyperglycemia (as defined above) could be referred to a lifestyle modification program in which the cost is borne by the individual participant. Given that there is no evidence that diabetes can be delayed or that clinically meaningful weight loss can be maintained in a community-based program (71, 72), asking the public to fund such an

intervention (through taxes or health care premiums) seems unwarranted.

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