ORIGINAL INVESTIGATION

Is Nondiabetic Hyperglycemia a Risk Factor for Cardiovascular Disease?

A Meta-analysis of Prospective Studies

Emily B. Levitan, ScB; Yiqing Song, MD; Earl S. Ford, MD, MPH; Simin Liu, MD, ScD

Background: Although hyperglycemia increases the risk of cardiovascular disease (CVD) in diabetic patients, the risk associated with blood glucose levels in the nondiabetic range remains unsettled.

Methods: We identified 38 reports in which CVD incidence or mortality was an end point, blood glucose levels were measured prospectively, and the relative risk (RR) and information necessary to calculate the variance were reported comparing groups of nondiabetic people. These reports were prospective studies, published in English-language journals. First author, publication year, participant age and sex, study duration, CVD end points, glucose assessment methods, control for confounding, range of blood glucose levels, RR, and confidence intervals (CIs) or *P* values were extracted. Using a random effects model, we calculated pooled RRs and 95% CIs.

Results: The group with the highest postchallenge blood glucose level (midpoint range, 150-194 mg/dL [8.3-10.8 mmol/L]) had a 27% greater risk for CVD compared with the group with the lowest level (midpoint range, 69-107 mg/dL [3.8-5.9 mmol/L]) (RR, 1.27 [95% CI, 1.09-1.48]). The results were similar when combining studies regardless of type of blood glucose assessment (RR, 1.36 [95% CI, 1.23-1.52]) and when using strict criteria for exclusion of diabetic subjects (RR, 1.26 [95% CI, 1.11-1.43]). Adjustment for CVD risk factors attenuated but did not abolish this relationship (RR, 1.19 [95% CI, 1.07-1.32]). The RR was greater in cohorts including women than in cohorts of men (RR, 1.56 vs 1.24 [*P*=.03]).

Conclusion: Blood glucose level is a risk marker for CVD among apparently healthy individuals without diabetes.

Arch Intern Med. 2004;164:2147-2155

Author Affiliations: Division of Preventive Medicine, Harvard Medical School and Brigham and Women's Hospital (Ms Levitan and Drs Song and Liu), and Department of Epidemiology, Harvard School of Public Health (Ms Levitan and Drs Song and Liu), Boston, Mass; and Division of Adult and Community Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Ga (Dr Ford).
Financial Interest: None.

INCREASING LEVELS OF GLYCEMIA among patients with diabetes mellitus (DM) is associated with increasing risk of cardiovascular disease (CVD).[1-3] Recent follow-up data from the Diabetes Control and Complications Trial support the notion that intensive glycemic control in patients with DM can slow atherosclerosis.[4] The current guidelines for diagnosis of DM were developed primarily on the basis of the blood glucose level threshold for microvascular complications, however.[5,6] The blood glucose level threshold for CVD may be different, or there may be no threshold.[7-9]

Numerous studies have examined whether blood glucose levels in the nondiabetic range are associated with increased risk of CVD, but results have not been consistent. In 1979, a collaborative study of 15 populations found conflicting results between populations,[9] but a subsequent meta-analysis of all available data to 1996 concluded that elevated blood glucose level was associated with risk in people without DM.[10] However, several interesting and clinically important questions about the glycemia-CVD relationship remain unanswered. First, although DM is a stronger risk factor in women than men, it is unclear whether the sex difference extends to nondiabetic hyperglycemia. Second, although glycemic control often decreases with age, it is not known whether elevated blood glucose levels in the elderly are associated with the same risk as in middle-aged individuals and whether different types of hyperglycemia are equally deleterious at all ages.[11] Third, hyperglycemia is associated with and potentially confounded by risk factors for CVD, including high blood pressure, dyslipidemia, obesity, and a sedentary lifestyle.[9,12] Whether hyperglycemia is a risk marker independent of other metabolic abnormalities is still unknown.[13] Finally, the different methods of glucose assessment (fasting or postchallenge glucose level or glycosylated hemoglobin level) may have contributed to the heterogeneous results in published studies. To explore these is-

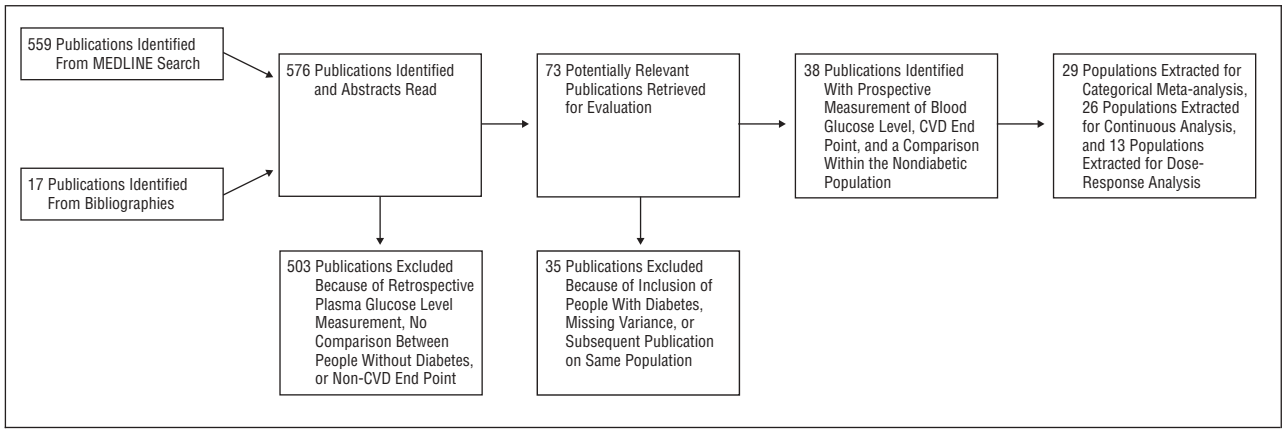

Figure 1. Summary of the publication selection process. CVD indicates cardiovascular disease.

sues, we conducted a systematic review and meta-analysis of all available prospective studies.

METHODS

STUDY SELECTION

We searched MEDLINE and National Institutes of Health Computer Retrieval of Information on Scientific Projects using keywords and medical subject headings relating to blood glucose and CVD (**Figure 1**). The bibliographies of retrieved articles were examined to ensure that all relevant, English-language articles up to May 2003 were identified. End points of interest included incidence of or mortality due to myocardial infarction, coronary heart disease, stroke, and CVD. Studies must have excluded people with known DM or included them as a separate group. The exclusion could be determined by results of a baseline assessment of blood glucose level or a previous diagnosis. Studies could have measured glucose level from any blood fraction. A total of 576 publications were identified, of which 17 reports were identified from bibliographies. Most articles were excluded after reading the abstract because they measured the blood glucose level retrospectively, did not have a comparison between groups without DM, or used CVD risk factors as end points. Of the 73 articles retrieved for full review, we further excluded 35 articles after complete reading. The reasons for exclusion include (1) multiple publications on the same cohort (n=11), (2) inability to separate people with and without DM (n=13), and (3) nonreporting of information required to calculate the standard error (n=11). The most recent publication on each study population including all necessary information was selected for each of the planned analyses. Two independent investigators reviewed the literature and identified eligible studies. The final data set of 38 independent study populations included 29 study populations that compare the top glycemia category with the bottom one and 26 study populations that examined blood glucose level as a continuous risk marker.

DATA EXTRACTION

Two independent investigators (E.B.L. and Y.S.) gathered the following information using a standardized data extraction form with differences resolved by discussion: lead author, number of participants, number of CVD events, study duration, age range, percentage of men in the study population, types of CVD end points, control for CVD risk factors, blood glucose level measurement, blood glucose level range in all categories, relative risk (RR) comparing the upper and lower categories of blood glucose level, and 95% confidence interval (CI) or *P* value. If the upper end of the range of blood glucose level was not reported, we assumed that the cutoff was the current diagnostic criteria for diabetes. If the lower end of the range was not reported, we assumed that it was 55 mg/dL (3.1 mmol/L) when symptoms of hypoglycemia begin to manifest (60 mg/dL [3.3 mmol/L] for autonomic effects and 50 mg/dL [2.8 mmol/L] for brain dysfunction).[14] Relative risks or β coefficients were also extracted from studies that assumed that blood glucose level was linearly related to CVD risk. Results for subcohorts were extracted as independent populations.

STATISTICAL ANALYSIS

To achieve a normal distribution, we transformed RRs comparing the highest with the lowest glycemia category by means of a natural log scale. The standard errors of the transformed RRs were calculated from reported 95% CIs or *P* values. We used random-effects models to calculate summary RRs to account for heterogeneity across individual studies. For the primary analysis, we used the most inclusive CVD end point and selected the exposure measures with the following preference: (1) blood glucose level after glucose load (postchallenge), (2) fasting blood glucose level, (3) glycosylated hemoglobin level, and (4) nonfasting (casual) blood glucose level. Sensitivity analyses were performed to examine whether the exposure measure and end point selected would markedly change the results. Through stratified analysis, we further examined sex, age, adjustment for traditional CVD risk factors, method of blood glucose level measurement, and type of CVD end point as potential sources of heterogeneity. To be considered as adjusted for CVD risk factors, studies must have adjusted for 2 or more of the following: blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, body mass index, smoking, and physical activity. We confirmed between-group heterogeneity using meta-regression.[15] We also used meta-regression to explore the relationship between the natural log RR and study duration. To examine whether increased CVD risk was due to inclusion of people with undiagnosed DM, we conducted a subgroup analysis of studies that used baseline blood glucose level measurements and the current definitions of DM (≥126 mg/dL [≥7.0 mmol/L] for fasting blood glucose level or ≥200 mg/dL [≥11.1 mmol/L] 2 hours after a 75-g glucose load)[5,6] as exclusion criteria. Publication bias was assessed by means of a funnel plot. We performed additional analyses of publications that reported β coefficients or RRs considering blood glucose level as a continuous risk marker. We used studies that reported 3 or more categories of nondiabetic blood glu-

cose level to examine the dose-response curve.[16] We estimated the average glycemia level by the midpoint of each reported range. We then divided the range of nondiabetic blood glucose levels under pre-1997 criteria (55-140 mg/dL [3.1-7.8 mmol/L] for fasting blood glucose level and 55-200 mg/dL [3.1-11.1 mmol/L] for postchallenge glucose level) into 5 equally sized intervals. We assigned the RRs from each study into 1 of these intervals on the basis of the average glycemia level. We calculated the random-effects pooled RR for each interval and fit a binomial regression line. All calculations were performed using STATA version 8 software (STATA Corporation, College Station, Tex).

RESULTS

The 29 study populations that compared the highest with the lowest category of glycemia consisted of 194 658 participants with a mean follow-up duration of 12.0 years (range, 4-23 years) and at least 6551 cardiovascular events. Women made up 17% of the total population (33 430 participants, approximately 1000 events). Thirteen studies reported postchallenge glucose levels with a variety of glucose loads and sampling times[17-26]; 18 reported fasting glucose levels[19,22,24-35]; 5 reported casual glucose levels[36-39]; and 3 reported glycosylated hemoglobin levels (**Table 1**).[19,40] The midpoint of the upper blood glucose level category ranges from 150 to 194 mg/dL (8.3-10.8 mmol/L) for postchallenge glucose level, 97 to 130 mg/dL (5.4-7.2 mmol/L) for fasting glucose level, 156 to 174 mg/dL (8.7-9.7 mmol/L) for casual glucose level, and 6.9% to 7.8% for glycosylated hemoglobin level. The midpoint of the lower category of glucose level ranges from 69 to 107 mg/dL (3.8-5.9 mmol/L) for postchallenge glucose level, 66 to 90 mg/dL (3.7-5.0 mmol/L) for fasting glucose level, 72 to 98 mg/dL (4.0-5.4 mmol/L) for casual glucose level, and 4.2% to 5.1% for glycosylated hemoglobin level. Of the studies that report blood glucose level as a continuous exposure, 17 assess postchallenge glucose level (65 770 participants, 2940 events),[11,17,40-49] 9 assess fasting glucose level (13 815 participants, 643 events),[11,34,49-52] 2 assess glycosylated hemoglobin level (4634 participants, 98 events),[11,40] and 4 assess casual glucose level (28 689 participants, 870 events) (**Table 2**).[36,37,53]

Using a random-effects model and combining studies with various types of glycemia assessment, we found that people in the top category of blood glucose level had a risk of CVD that was 36% greater than those in the bottom category (pooled RR, 1.36 [95% CI, 1.23-1.52]; $P<.001$ for heterogeneity) (**Figure 2**). There were no appreciable differences in the pooled RRs obtained in sensitivity analyses using different algorithms to select blood glucose level measurements and end points. Restricting the analysis to the 13 studies that used current diagnostic definitions of DM as exclusion criteria[18-20,22,24,25,30,34,35] did not significantly alter the pooled RR (RR for current criteria, 1.26 [95% CI, 1.11-1.43]; RR for all other studies, 1.48 [95% CI, 1.25-1.75]; $P=.14$ for between-group heterogeneity). The positive association between blood glucose levels and CVD risk was more apparent in cohorts of women and mixed-sex cohorts than in cohorts of men only (**Table 3**). However, the relationship did not appear to differ by age for the main analysis and is not significantly different within studies that assessed fasting and postchallenge blood glucose levels. In our meta-regression analysis that included follow-up period as a study-level covariate, differences in study duration did not affect pooled estimates materially. A 1-year increase in study duration was associated with a 0.01-U decrease in log RR (95% CI, −0.03 to 0.002; $P=.10$). Stratification by adjustment for traditional CVD risk factors attenuated but did not fully explain the blood glucose level effect.

The pooled RRs were 1.27 (95% CI, 1.13-1.43) comparing the top and bottom categories of glycemia from studies measuring fasting blood glucose level and 1.27 (95% CI, 1.09-1.48) from studies measuring postchallenge blood glucose level. Studies considering blood glucose level as a continuous exposure showed compatible results. One study reporting postchallenge blood glucose level as a continuous exposure was a heavily weighted outlier.[48] Removing that study increased the overall pooled RR for a 20-mg/dL (1.1-mmol/L) increase in postchallenge blood glucose level to 1.05 (95% CI, 1.04-1.07) and the pooled RR for cohorts of men to 1.04 (95% CI, 1.02-1.06). The difference in the pooled RR for cohorts of men and the pooled RR for cohorts of women and mixed-sex cohorts remained significant ($P=.03$). Although the sample size was quite small and the results were not statistically significant, glycosylated hemoglobin A_{1c} level appeared to be a good predictor of CVD events (RR, 1.70 [95% CI, 0.99-2.94]). Casual blood glucose level also was a strong predictor of CVD.

Twelve studies reporting fasting glucose level[21,26,29,31,32,34,40,51] and 6 studies reporting postchallenge glucose level[17,21,26,40] were available for estimating the dose-response curve (**Figure 3**). Postchallenge glucose level appears to be linearly related to CVD across the nondiabetic range, whereas fasting blood glucose level shows a possible threshold effect at 100 mg/dL (5.6 mmol/L).

Figure 4 shows a funnel plot for the visual assessment of publication bias. The plot shows slightly more data points from small studies above the horizontal line (representing the pooled estimate of log RR), indicating a possible minor publication bias favoring studies with positive outcomes.

COMMENT

Our results extend the relationship between blood glucose level and CVD into the nondiabetic range. Although postchallenge blood glucose level has a linear relationship with CVD risk in the nondiabetic range, a possible threshold effect with fasting blood glucose level appears to be around 100 mg/dL (5.6 mmol/L). This finding supports the newly revised criteria by the American Diabetes Association for the diagnosis of impaired fasting glucose level.[54] Women may have a greater CVD risk associated with hyperglycemia than men in these populations without apparent DM, consistent with a similar sex difference previously seen in people with DM; however, few studies examined the relationship in cohorts of women only. The mechanism for the apparent sex-specific relationship between DM and CVD is still un-

Table 1. Characteristics of Study Populations That Compare the Top and Bottom Categories of Glycemia

Source	Participants (No. of Events)	Duration, y	Age, y	Men, %	Outcome	Control for Risk Factors	Glycemia Assessment Method	Highest/Lowest Glycemia Category*	RR (95% CI)
Lapidus et al,[27] 1985	1462 (1)	12	38-60	0	MI incidence	No	Fasting	≥98/<98	1.8 (0.2-14.7)
Ohlson et al,[28] 1986	832 (106)	17	50	100	CHD incidence	No	Fasting	102-125/<102	1.3 (0.7-3.3)
Vaccaro et al,[17] 1992	838 (144)	19	34-65	100	CVD mortality	No	Postchallenge	194/97 (mean)	1.96 (1.11-3.45)
Yarnell et al,[29] 1994	4519 (219)	4	45-59	100	CHD incidence	Yes	Fasting	122-139/≤85	2.9 (1.2-6.6)
Haheim et al,[36] 1995	16021 (80)	18	40-49	100	Stroke mortality	No	Casual	>112/≤90	1.18 (0.57-2.49)
Casiglia et al,[30] 1996	2079 (341)	10	65-91	39	CVD mortality	No	Fasting	121-139/<121	1.44 (NR)
Fujishima et al,[18] 1996	2167 (164)	5	40-79	43	CVD mortality	No	Postchallenge	140-199/>140	1.9 (1.2-3.2)
Park et al,[19] 1996									
Men	549 (NR)	8	55-90	100	CVD mortality	Yes	HbA_{1c}	6.6-8.6/3.6-6.5	1.10 (0.61-1.97)
							Fasting	108-136/51-107	0.75 (0.39-1.46)
							Postchallenge	151-199/33-150	0.83 (0.47-1.45)
Women	690 (NR)	8	55-92	0	CVD mortality	Yes	HbA_{1c}	6.7-8.9/3.4-6.6	2.61 (1.40-4.88)
							Fasting	105-133/44-87	1.30 (0.61-2.81)
							Postchallenge	159-199/43-158	1.01 (0.51-2.00)
Cremer, et al,[32] 1997	5639 (299)	10	40-59	100	MI incidence	No	Fasting	≥111/<86	1.6 (1.1-2.2)
Folsom et al,[31] 1997									
Men	5648 (166)	5.5	45-64	100	CHD incidence	Yes	Fasting	115-139/<91	1.08 (1.08-1.90)
Women	7798 (63)	5.5	45-65	0	CHD incidence	Yes	Fasting	115-139/<91	0.53 (0.18-1.55)
Lowe et al,[20] 1997									
Black	594 (61)	22	35-64	100	CVD mortality	Yes	Postchallenge	159-199/<159	1.17 (0.66-2.1)
White	9830 (1043)	22	35-64	100	CVD mortality	Yes	Postchallenge	159-199/<159	1.04 (0.91-1.19)
Balkau et al,[21] 1998†	10 025 (1073)	20	44-55	100	CVD mortality	Yes	Postchallenge	>100/≤82	1.08 (0.79-1.50)
Bjornholt et al,[33] 1999	1973 (249)	22	40-59	100	CVD mortality	Yes	Fasting	86-109/52-85	1.40 (1.04-1.80)
de Vegt et al,[40] 1999‡	2363 (98)	8	50-75	46	CVD mortality	Yes	HbA_{1c}	>6.5/<5.2	1.79 (0.77-4.16)
Hart et al,[37] 1999									
Men	4768 (200)	20	45-64	100	Stroke mortality	No	Casual	>129/≤129	1.31 (0.75-2.30)
Women	5806 (264)	20	45-64	0	Stroke mortality	No	Casual	>122/≤122	2.18 (1.44-3.29)
Rodriguez et al,[23] 1999	6514 (NR)	23	48-68	100	CHD incidence	Yes	Postchallenge	151-224/<151	1.08 (0.92-1.27)
Tominaga et al,[22] 1999	2398 (30)	6	≥40	44	CVD mortality	No	Fasting	110-125/<110	1.14 (0.35-3.73)
							Postchallenge	140-199/<140	2.22 (1.08-4.58)
Wannamethee et al,[38] 1999	7551 (276)	16.8	40-59	100	Stroke incidence	Yes	Casual	≥147/<88	1.86 (1.11-3.13)
Simons et al,[34] 2000									
Men	1048 (NR)	9.4	≥60	100	CHD incidence	No	Fasting	95-107/57-81	1.08 (0.77-1.51)
Women	1371 (NR)	9.4	≥60	0	CHD incidence	No	Fasting	95-107/57-81	1.52 (1.08-2.15)
DECODE Study Group,[24] 2001									
Men	14 376 (NR)	8.8	30-89	100	CVD mortality	Yes	Fasting	110-125/<110	1.03 (0.85-1.25)
							Postchallenge	140-199/<140	1.34 (1.12-1.60)
Women	6686 (NR)	8.8	30-89	0	CVD mortality	Yes	Fasting	110-125/<110	1.53 (0.81-2.90)
							Postchallenge	140-199/<140	1.28 (0.88-1.86)
Saydah et al,[25] 2001	3092 (661)	16	30-74	46	CVD mortality	Yes	Fasting	110-125/<110	0.65 (0.31-1.34)
							Postchallenge	140-199/<140	0.93 (0.57-1.51)
Henry et al,[35] 2002	63 443 (171)	8	21-60	100	CVD mortality	Yes	Fasting	110-125/70-109	1.44 (1.09-1.90)
Klein et al,[39] 2002	2971 (176)	4.8	43-86	43	CVD incidence	No	Casual	≥140/<140	2.31 (1.40-3.82)
Smith et al,[26] 2002	4014 (764)	8.5	≥65	40	CVD incidence	No	Fasting	≥112/≤92	1.42 (1.14-1.76)
							Postchallenge	≥182/≤103	1.90 (1.51-2.39)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DECODE, Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe; HbA_{1c}, glycosylated hemoglobin level; MI, myocardial infarction; NR, not reported; RR, relative risk.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

*Glucose levels are measured as percentages for HbA_{1c}; all other measurements are reported as milligrams per deciliter (all reported glucose loads and sampling times).

†Whitehall population only was included in the main analysis. Other populations in this report contributed to the dose-response analysis and are included in the more recent DECODE Study.

‡Includes subgroup analysis of HbA_{1c} and dose-response analysis only. Data for postchallenge and fasting glucose levels for this population are included in the DECODE Study.

clear.[12] Hyperglycemia in women may be more associated with other CVD risk factors than in men. This finding is supported by a meta-analysis that reported that significant differences in CVD risk between men and women disappeared after extensive control of other CVD risk factors.[55] However, other studies reported that adjustment for CVD risk factors does not explain the sex difference, suggesting that hyperglycemia may abolish the protective effects of being female on CVD risk.[56]

Our subgroup analysis indicates that blood glucose level may be a clinically significant risk marker, associated with a 19% increase in CVD risk independent of traditional risk factors. Although these data cannot exclude the possibility that the increase in CVD risk may

Table 2. Characteristics of Study Populations That Consider the Linear Relationship of Glycemia With CVD

Source	Participants (No. of CVD Events)	Duration, y	Age, y	Men, %*	Outcome	Control for Risk Factors	Glycemia Assessment Method	β (SE)†
Da Silva et al,[41] 1979	1469 (12)	5	40-59	100	CVD mortality	Yes	Postchallenge	0.010 (0.012)
Ducimetiere et al,[42] 1979	6373 (41)	5	42-53	100	CVD mortality	Yes	Postchallenge	0.003 (0.003)
Fuller et al,[43] 1979	15 344 (275)	5	40-64	100	CVD mortality	Yes	Postchallenge	0.003 (0.003)
Reunanen et al,[44] 1979	3212 (64)	4	40-59	100	CVD mortality	Yes	Postchallenge	−0.001 (0.003)
Schroll and Hagerup,[50] 1979	375 (44)	10	50	100	CVD incidence	Yes	Fasting	−0.017 (0.015)
Stamler et al,[45] 1979‡	1589 (166)	15	42-58	100	CVD mortality	Yes	Postchallenge	−0.002 (0.003)
Stenhouse et al,[46] 1979	603 (21)	11	40-59	100	CVD mortality	Yes	Postchallenge	−0.0003 (0.0003)
Barrett-Connor et al,[51] 1984								
Men	1610 (166)	9	40-79	100	CVD mortality	Yes	Fasting	0.012 (0.006)
Women	2015 (69)	9	40-79	0	CVD mortality	Yes	Fasting	0.017 (0.009)
Wilson et al,[53] 1991, women	2094 (326)	10	45-84	0	CVD incidence	No	Casual	0.005 (0.002)
Vaccaro et al,[17] 1992	843 (144)	19	34-65	100	CVD mortality	Yes	Postchallenge	0.005 (0.003)
Tomas-Abadal et al,[52] 1994	1059 (91)	20	30-59	100	CHD incidence	Yes	Fasting	0.009 (0.004)
Haheim et al,[36] 1995	16 021 (80)	18	40-49	100	Stroke mortality	No	Casual	0.001 (0.006)
Orencia et al,[47] 1997								
Men aged 18-39 y	10 269 (171)	22	18-39	100	CVD mortality	Yes	Postchallenge	0.003 (0.002)
Men aged 40-59 y	7993 (870)	22	40-59	100	CVD mortality	Yes	Postchallenge	0.002 (0.001)
Men aged 60-74 y	1240 (345)	22	60-74	100	CVD mortality	Yes	Postchallenge	0.001 (0.001)
Women aged 40-59 y	6319 (289)	22	40-59	0	CVD mortality	Yes	Postchallenge	0.002 (0.001)
Women aged 60-74 y	932 (171)	22	60-74	0	CVD mortality	Yes	Postchallenge	0.004 (0.001)
De Vegt et al,[40] 1999	2199 (98)	8	50-75	46	CVD mortality	Yes	HbA_{1c}	−0.029 (0.236)
							Postchallenge	0.003 (0.004)
Hart et al,[37] 1999								
Men	4768 (200)	20	45-64	100	Stroke mortality	No	Casual	0.004 (0.002)
Women	5806 (264)	20	45-64	0	Stroke mortality	No	Casual	0.009 (0.002)
Simons et al,[34] 2000	1371(NR)	9.4	≥60	0	CHD incidence	No	Fasting	0.016 (0.006)
Agewall,[48] 2001	113 (10)	6.3	50-72	100	CVD mortality	No	Fasting	0.019 (0.033)
						Yes	Postchallenge	0.025 (0.012)
Meigs et al,[11] 2002	3370 (118)	4	26-82	46	CVD incidence	Yes	HbA_{1c}	0.199 (0.087)
							Fasting	0.006 (0.002)
							Postchallenge	0.004 (0.001)
Stern et al, 2002[49]								
Men	1693 (95)	7.5	25-64	100	CVD incidence	No	Fasting	0.010 (0.004)
						Yes	Postchallenge	0.001 (0.002)
Women	2209 (50)	7.5	25-64	0	CVD incidence	No	Fasting	0.010 (0.003)
						Yes	Postchallenge	0.002 (0.002)

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HbA_{1c}, glycosylated hemoglobin; NR, not reported; SE, standard error.
SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.
*Data represent the percentage of the study that was male. In studies that included only women, the value is zero.
†For 1-mg/dL increase of fasting, postchallenge, and casual glucose levels, and 1% increase for HbA_{1c}.
‡Indicates Western Electric Co Study only.

be due to other adverse metabolic conditions, including insulin resistance and hyperinsulinemia, they indicate that blood glucose level, even in the nondiabetic range, is a significant risk marker for the future development of CVD. Signficant in vitro and animal study evidence implicates elevated blood glucose levels in the development of CVD, although the exact mechanism of cardiovascular damage associated with glycemia is not clear. Detrimental effects of elevated glycemia levels include nonenzymatic glycosylation of proteins, increased metabolism of glucose through the polyol and glucosamine pathways, and generation of free radicals.[57,58] Glycosylation of low-density lipoprotein makes it more oxidizable and more atherogenic,[57] and advanced glycosylation end products can cross-link proteins, particularly in the extracellular matrix of the vascular walls.[59] Metabolism of excess glucose by secondary pathways can also alter cell function by altering signal transduction and changing the oxidative potential in cells. This may contribute to general cell damage and dysfunction.[57] These pathways can also activate tissue-specific protein kinase C.[58] Increased protein kinase C activity decreases fibrinolysis and nitric oxide levels and increases cell proliferation and coagulation, contributing to CVD development.[57,58]

There has been an ongoing debate about which of the interrelated defects in glucose metabolism and regulation is responsible for the increased risk of CVD.[57] Postprandial hyperglycemia, tested clinically by means of postchallenge glucose assessment, is suspected to be particularly harmful and occurs long before the elevation of the fasting glucose level.[57] In our study, people in the top categories of postchallenge and fasting glucose levels had similarly increased risks of CVD; however, the CVD risk increased more steeply for increasing fasting blood glucose level than for postchallenge glucose level, perhaps because the nondiabetic range is greater for the postchal-

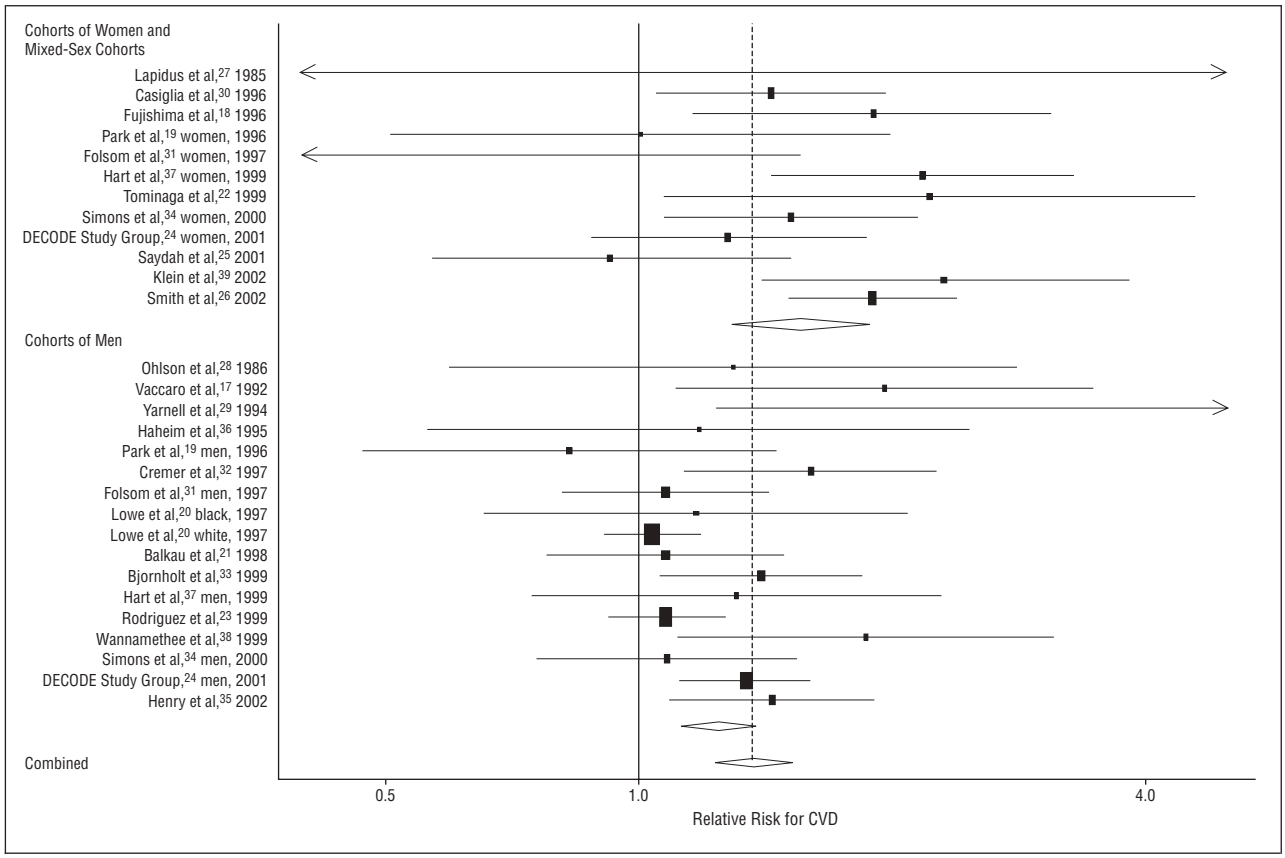

Figure 2. Relative risks for cardiovascular disease (CVD) comparing the highest with the lowest glycemia categories stratified by sex. Size of the solid squares is inversely proportional to the variance of the study estimate. Arrows represent error bars that continue beyond the scale of the figure, and diamonds represent the random-effects pooled relative risk and 95% confidence interval overall and for analyses by sex. The dashed line is drawn at the overall pooled estimate.

lenge glucose level. Glycosylated hemoglobin level, which measures relatively long-term glycemia, appears to be a reasonable alternative to measuring postchallenge or fasting blood glucose level. Glycosylated hemoglobin level was predictive of CVD across the whole range of values in 1 cohort and had a higher predictive value for mortality than other CVD risk factors.[60] In this population, there was a suggestion, although not significant, that the glycosylated hemoglobin level is useful for the prediction of CVD. Although casual glucose level was an unexpectedly strong predictor of CVD, given the intra-individual variability inherent in this test, the strong association may be due to misclassification of individuals with undiagnosed DM.

Recently, the STOP Non–Insulin-Dependent Diabetes Mellitus Trial found that reducing postprandial hyperglycemia with acarbose, an α-glucosidase inhibitor, reduced incidence of CVD by 49% in 1368 people with impaired glucose tolerance who were followed up for 3.3 years.[61] Dietary changes such as low glycemic load foods can also reduce glycemic burden, shown by a recent meta-analysis,[62] as can exercise and hypoglycemic medications. The American Diabetes Association does not recommend measurement of postchallenge glucose levels for screening because of the expense, inconvenience, and intraindividual variability of the test.[5] Our study does not support the notion that the postchallenge blood glucose level is superior to the fasting blood glucose level for predicting CVD in the nondiabetic range, although the two tests may identify different individuals at increased risk, and some individuals who are classified as nondiabetic by fasting blood glucose level may be classified as diabetic by postchallenge glucose level. In particular, it has been suggested that age may modify the glycemic response due to insulin resistance and that hyperglycemia may shift from mainly fasting hyperglycemia in younger subjects to mainly postchallenge hyperglycemia in older subjects.[11] Results from our analysis did not support this hypothesis, although the categorization of populations by whether or not they included individuals older than 60 years is not optimal for detecting a difference.

The magnitude of the glycemia association with CVD risk in our study is consistent with that previously reported.[10] In addition, we have investigated heterogeneity between studies due to differences in sex, age range, and control for CVD risk factors. We have also examined different types of glycemia assessment, including casual blood glucose level and preliminary results for glycosylated hemoglobin level.

We found substantial differences across studies included in this analysis. First, the methods, blood fractions, and time frame postchallenge used to assess glycemia varied across studies. Second, the ranges for the top and bottom glucose categories varied across studies. Third, studies reported different end points, although selection of different end points did not affect our results in a sensitivity analysis (results not shown). Moreover, changes in the definition of diabetes and methods to exclude people with DM used across the studies may contribute to the het-

Table 3. Pooled RR for CVD According to Study Characteristics

Group	Categorical Pooled RR (95% CI)*	No. of Studies	Between-Group Heterogeneity, *P* Value	Continuous Pooled RR (95% CI)†‡	No. of Studies	Between-Group Heterogeneity, *P* Value
All studies	1.36 (1.23-1.52)	29		1.04 (1.02-1.06)	17	
Sex			.03			.01
Female and mixed studies	1.56 (1.30-1.88)	12		1.08 (1.05-1.10)	5	
Male studies	1.24 (1.12-1.37)	17		1.03 (1.00-1.05)	12	
Adjusted for CVD risk factor			<.001			NA
Yes	1.19 (1.07-1.32)	15		1.04 (1.02-1.06)	17	
No	1.64 (1.46-1.86)	14		NA	0	
Study age category						
Middle-aged (<60 y)	1.39 (1.21-1.60)	7	.82			
Middle-aged and older	1.36 (1.19-1.55)	22				
Middle-aged (fasting)	1.45 (1.23-1.72)	4	.10	1.00 (0.62-1.62)	2	.46
Middle-aged and older (fasting)	1.21 (1.04-1.40)	14		1.20 (1.13-1.28)	7	
Middle-aged (postchallenge)	1.08 (0.78-1.49)	1	.32	1.02 (0.99-1.06)	8	.07
Middle-aged and older (postchallenge)	1.30 (1.10-1.53)	12		1.06 (1.04-1.09)	9	
Glycemia assessment method			NA			NA
Fasting glucose level	1.27 (1.13-1.43)	18		1.20 (1.13-1.27)	9	
Postchallenge glucose level	1.27 (1.09-1.48)	13		1.04 (1.02-1.07)	17	
Casual glucose level	1.84 (1.45-2.33)	5		1.12 (1.06-1.19)	4	
Glycosylated hemoglobin level	1.70 (0.99-2.94)	3		1.19 (1.01-1.39)	2	

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; NA, not applicable; RR, relative risk.
SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.
*Determined by comparing the top and bottom categories of blood glucose level.
†The RR is associated with an increase of 1% in glycosylated hemoglobin level or 20 mg/dL in blood glucose level.
‡Subgroup analyses are based on postchallenge blood glucose levels unless otherwise specified.

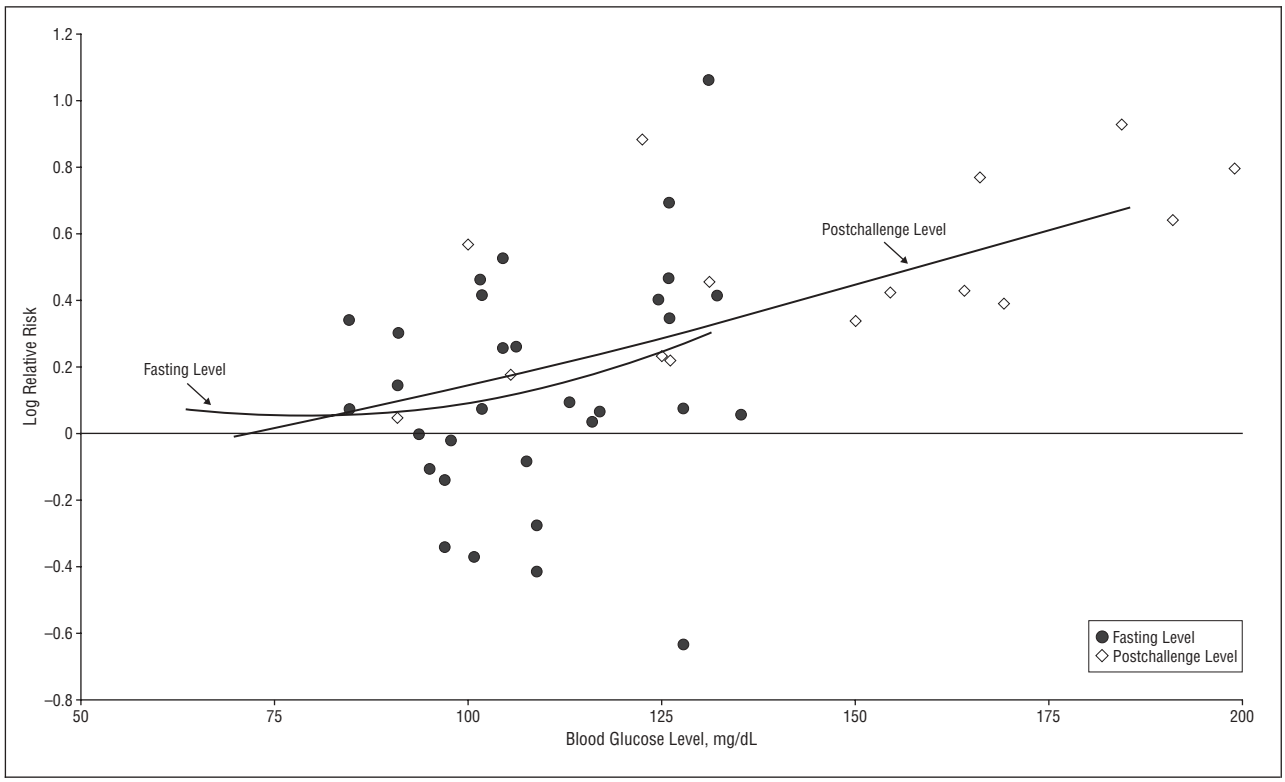

Figure 3. Dose-response relationship of cardiovascular disease with fasting and postchallenge blood glucose levels. To convert glucose to millimoles per liter, multiply by 0.0555.

erogeneity of these published results. However, in a sensitivity analysis of studies that did not include any individuals meeting the current criteria for diagnosis of DM, the pooled RR was not significantly different from the RR estimated from studies that could not apply those strict exclusion criteria. To account for these differences and iden-

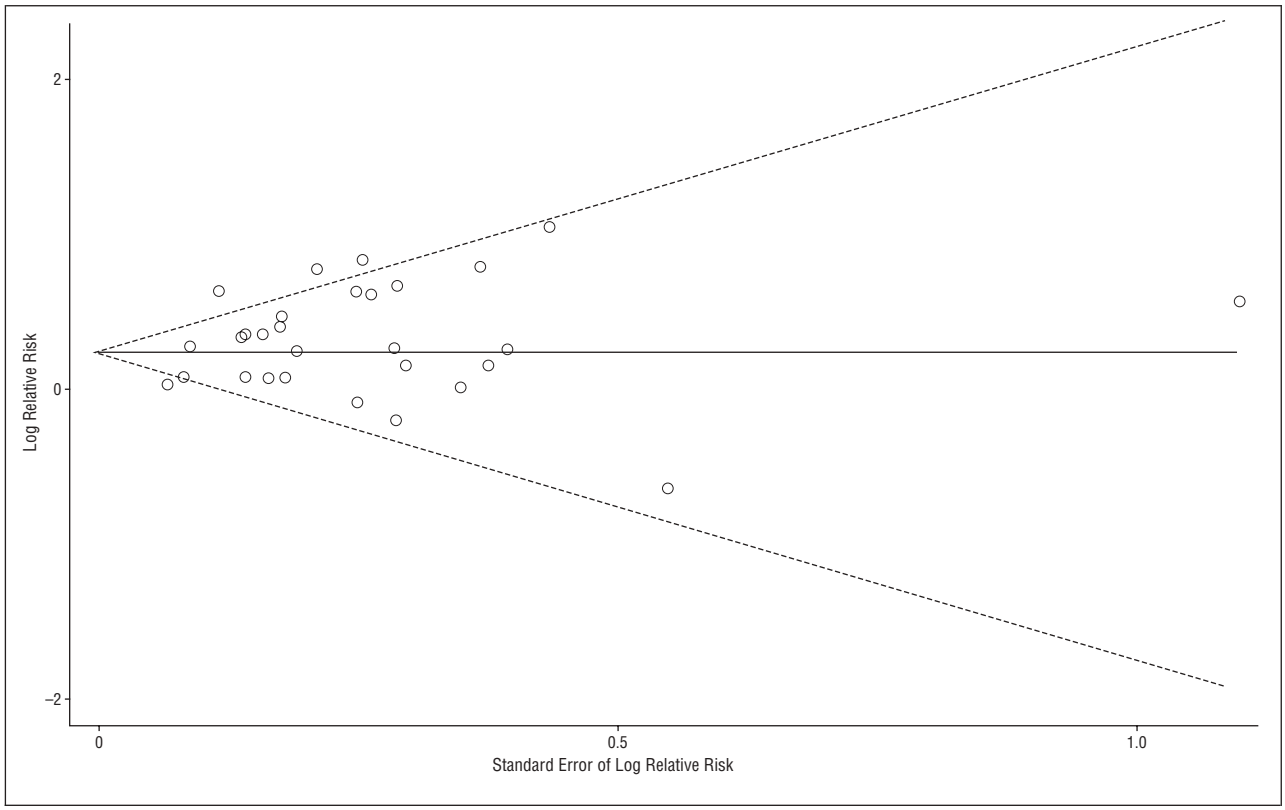

Figure 4. Funnel plot of log relative risks according to their standard errors. The horizontal solid line is drawn at the pooled log relative risk, and dashed lines represent the expected 95% confidence interval for a given standard error, assuming no between-study heterogeneity.

tify sources of heterogeneity, we also conducted meta-regression and stratified analyses. Although it is likely that DM and then CVD developed in some individuals with nondiabetic hyperglycemia, this does not change the conclusion that baseline hyperglycemia can predict CVD. The studies also varied in the CVD risk factors measured, and none measured insulin resistance or fasting insulin level, preventing the identification of hyperglycemia as an independent risk factor. Future studies that measure these risk factors are needed to determine whether nondiabetic hyperglycemia causes cardiovascular damage or shares common causes with CVD. Finally, as in many meta-analyses, there is evidence of some publication bias favoring positive studies.

In summary, our meta-analysis of 38 prospective studies that included 172 934 men and 44 216 women indicates that screening for blood glucose levels, even among those who are not suspected of having DM, may be useful for identifying individuals, particularly women, at increased risk of CVD.

Accepted for Publication: May 15, 2004.
Correspondence: Simin Liu, MD, ScD, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave E, Boston, MA 02215 (sliu@rics.bwh.harvard.edu).
Acknowledgment: We thank Jeffrey Bears, SM, Lynne Peeples, SM, and Justin Timbie for their help on an early version of this project.

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