Markers of Dysglycaemia and Risk of Coronary Heart Disease in People without Diabetes: Reykjavik Prospective Study and Systematic Review

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Abstract

Background: Associations between circulating markers of dysglycaemia and coronary heart disease (CHD) risk in people without diabetes have not been reliably characterised. We report new data from a prospective study and a systematic review to help quantify these associations.

Methods and Findings: Fasting and post-load glucose levels were measured in 18,569 participants in the population-based Reykjavik study, yielding 4,664 incident CHD outcomes during 23.5 y of mean follow-up. In people with no known history of diabetes at the baseline survey, the hazard ratio (HR) for CHD, adjusted for several conventional risk factors, was 2.37 (95% CI 1.79–3.14) in individuals with fasting glucose ≥7.0 mmol/l compared to those <7 mmol/l. At fasting glucose values below 7 mmol/l, adjusted HRRs were 0.95 (0.89–1.01) per 1 mmol/l higher fasting glucose and 1.03 (1.01–1.05) per 1 mmol/l higher post-load glucose. HRRs for CHD risk were generally modest and nonsignificant across tenths of glucose values below 7 mmol/l. We did a meta-analysis of 26 additional relevant prospective studies identified in a systematic review of Western cohort studies that recorded fasting glucose, post-load glucose, or glycated haemoglobin (HbA1c) levels. In this combined analysis, in which participants with a self-reported history of diabetes and/or fasting blood glucose ≥7 mmol/l at baseline were excluded, relative risks for CHD, adjusted for several conventional risk factors, were: 1.06 (1.00–1.12) per 1 mmol/l higher fasting glucose (23 cohorts, 10,808 cases, 255,171 participants); 1.05 (1.03–1.07) per 1 mmol/l higher post-load glucose (15 cohorts, 12,652 cases, 102,382 participants); and 1.20 (1.10–1.31) per 1% higher HbA1c (9 cohorts, 1639 cases, 49,099 participants).

Conclusions: In the Reykjavik Study and a meta-analysis of other Western prospective studies, fasting and post-load glucose levels were modestly associated with CHD risk in people without diabetes. The meta-analysis suggested a somewhat stronger association between HbA1c levels and CHD risk.

Please see later in the article for the Editors’ Summary.

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Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; HbA1c, glycated haemoglobin; HR, hazard ratio; ICD, International Classification of Diseases; RR, relative risk; SD, standard deviation.

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Introduction

Diabetes is an established risk factor for coronary heart disease (CHD). There is considerable interest in whether circulating markers of glucose metabolism are associated with risk of CHD in people without diabetes. Various measures of dysglycaemia have been assessed in long-term studies of CHD, notably: fasting glucose concentration (an indicator of steady-state glucose metabolism at the time of measurement); post-load glucose concentration (an indicator of immediate response to glycaemic stress); and glycated haemoglobin (HbA1c, an indicator of average blood glucose concentration over the previous 1–3 mo) [1,2]. It has been proposed that markers of dysglycaemia may be log-linearly and importantly associated with risk of subsequent vascular disease at all levels (including below the thresholds defining diabetes) [3–5], but available data are not conclusive. For example, the US Preventive Services Task Force recently stated that published prospective data on fasting glucose and CHD were “inconsistent” and had “serious limitations” [6].

We report new data from the population-based Reykjavik prospective study on associations of fasting and post-load glucose levels with CHD incidence across the range of glucose values. We also did a systematic review and meta-analysis of tabular data from 26 additional relevant Western cohorts [7–31]. In total, the current report considers data on 303,961 participants, including 16,982 incident CHD cases.

Methods

Participants in the Reykjavik Study

The Reykjavik study has been described in detail previously [32]. Men born during 1907–1934 and women born during 1908–1935 who were resident in Reykjavik, Iceland and its adjacent communities on 1 December 1966 were identified in the national population register and invited to participate during five stages of recruitment between 1967 and 1991. A total of 8,888 male and 9,681 female participants without a history of myocardial infarction agreed to take part (72% response rate). Nurses administered questionnaires, made physical measurements, recorded an electrocardiogram, and collected fasting blood samples (taken after ≥8 h of fasting) at baseline. All participants have been monitored subsequently by central registries for occurrence of major cardiovascular morbidity (based on WHO MONICA [Multinational Monitoring of Trends and Determinants in Cardiovascular Disease] or similar criteria) or cause-specific mortality (based on a death certificate with International Classification of Diseases [ICD] 9 codes 410–414), with a loss to follow-up of only about 0.6% to date. During mean follow-up of 23.5 y, nonfatal MI or fatal CHD was recorded in a total of 4,664 participants, of whom 4,490 (including 3,088 men and 1,402 women) had no history of diabetes at baseline. Data were not available on incidence of stroke, diabetes, or microvascular disease. The National Bioethics Committee and the Data Protection Authority of Iceland approved the study protocol, and participants gave informed consent.

Laboratory Methods

Fasting glucose measurement was carried out in fresh capillary whole blood within hours of blood sampling at the initial examination by a micro method on a Technicon AutoAnalyzer using a modification of the W. S. Hoffman method (coefficient of variation 4%) and standardised to the Hyland Normal Clinical Chemistry Control Serum (Nygaard A/S, Oslo) [33]. Post-load glucose levels were measured 60 and 90 min after ingestion of a 50 g glucose load. Lipid and other measurements involved standard assays, as previously described [32]. HbA1c measurements were not done.

Statistical Methods

The shapes of associations with CHD risk in the Reykjavik study were characterized by calculation of hazard ratios (HRs) across hundreds of glucose values, including the full range of glucose values observed. Cox proportional hazards regression models were adjusted for age, sex, smoking status, systolic blood pressure, total cholesterol, and body mass index (BMI). Ninety-five percent confidence intervals (95% CIs) were estimated from the variances that reflect the amount of information underlying each group (including the reference group) [34]. Subsidiary analyses corrected for regression dilution using serial glucose measurements made in 370 of the participants (mean interval: 12 y) [35]. In 18,333 participants without evidence of diabetes at baseline (i.e., no self-reported history and fasting blood glucose <7 mmol/l), HRs for CHD were calculated per 1 mmol/l higher glucose concentration. Impaired fasting glucose was defined using published guidelines [36]. Effect-modification was investigated by formal tests of interaction.

Systematic Review

Three of the current investigators (NS, RG, and SRKS) sought prospective studies published between January 1970 and September 2009 that had reported on associations of fasting blood glucose, post-load glucose, and/or HbA1c with incident CHD. Details of the search strategies and a flow diagram are provided in Text S1. Published studies were identified through electronic searches not limited to the English language (using MEDLINE, EMBASE, BIOSIS, and the Science Citation Index), by scanning reference lists of articles identified for all relevant studies (including review articles), and by hand searching of selected general medical journals (i.e., BMJ, JAMA, Lancet, NEJM, PLoS Medicine, Annals of Internal Medicine, Archives of Internal Medicine), cardiovascular/diabetes journals (i.e., Circulation, Diabetes, Diabetes Care, European Heart Journal, Journal of the American College of Cardiology), and epidemiological journals (i.e., American Journal of Epidemiology, International Journal of Epidemiology). Studies were eligible for inclusion if they: (1) did not select participants on the basis of having pre-existing vascular disease; (2) were located in Western Europe, North America, or Australasia (a restriction to reduce potential heterogeneity due to factors related to geographical location, e.g., ethnicity; see Discussion); (3) had more than 1 y of follow-up; and (4) reported on nonfatal MI (as defined by WHO MONICA or equivalent criteria, i.e., involving diagnosis based on clinical symptoms, electrocardiographic abnormalities, and/or cardiac biomarkers) and/or fatal CHD (defined by ICD criteria). Eligibility for inclusion of identified studies was considered by two investigators (RG and SRKS). Any disagreement was resolved by discussion and, if necessary, by the deciding vote of a third reviewer (NS).

A request for tabular data was sent to investigators of every eligible study identified. The following information was sought (excluding participants with a self-reported history of diabetes and/or fasting blood glucose ≥7 mmol/l at baseline), according to a uniform protocol: number of incident CHD outcomes recorded; relative risk (RR with 95% CI for CHD per unit higher dysglycaemia marker, initially after adjustment for age and sex only and then after additional adjustment for smoking status, systolic blood pressure, lipid concentrations, and BMI); the content of the glucose load and interval before post-load venipuncture; number of participants with resurvey measurements; interval between such measurements; and degree of long-term within-person variability of dysglycaemia markers (Table S1). Accuracy of the information supplied was cross-checked against published
(a) Across tenths of fasting glucose

(b) Across tenths of fasting glucose, with the final tenth further divided into fifths

(c) Across tenths of fasting glucose, with the final tenth further divided into tenths
data. In the few instances of apparent discrepancy, resolution was achieved through consultation with study investigators.

**Meta-analysis**

Summary RRs for CHD per unit higher dysglycaemia marker were calculated by pooling study-specific estimates using a random effects model. Analyses involved only within-study comparisons. As regards units of analysis used, 1 mmol/l higher fasting glucose corresponds approximately to 1-standard deviation (SD) higher levels; 1 mmol/l higher post-load glucose corresponds approximately to 2-SD higher levels; and 1% higher HbA1c corresponds approximately to 1-SD higher levels. Consistency of findings was assessed by standard χ² tests and the I² statistic [37]. Diversity at the study level was investigated by grouping studies by recorded characteristics and by meta-regression (including study size and duration of follow-up as continuous variables). Small-study effects were investigated [30].

**Results**

**Reykjavik Study**

Baseline conventional risk factors were significantly higher in those who subsequently recorded incident CHD than in non-cases, as were fasting and 1-h post-load glucose levels (Table S2). Fasting and 1-h post-load glucose levels were each significantly correlated with several conventional risk factors and with each other (Table S3). In people without diabetes at baseline, serial measurements yielded intra-class correlation coefficients of 0.61 (95% CI 0.54–0.67) for fasting blood glucose, 0.50 (0.42–0.57) for 1-h post-load glucose, 0.59 (0.51–0.67) for total cholesterol, and 0.65 (0.54–0.77) for systolic blood pressure. In people who had no history of diabetes at baseline, HR for CHD—adjusted for age, sex, recruitment period, smoking status, systolic blood pressure, total cholesterol, and BMI (hereafter, “adjusted HR”)—was 2.37 (1.79–3.14) in those with fasting glucose ≥7.0 mmol/l compared with those <7.0 mmol/l. HR was 1.67 [1.36–2.02] with fasting glucose ≥6.1 mmol/l compared with those <6.1 mmol/l, a definition of diabetes proposed for studies involving capillary whole blood samples [39]. In analyses across tenths of fasting glucose values, adjusted HRs for CHD were generally weak and nonsignificant at levels below 7 mmol/l (Figure 1). Findings were broadly similar for 1-h post-load glucose levels (Figure 2) and in analyses that: adjusted for age and sex only (Figure S1); corrected for regression dilution (Figure S2); assessed 90-minute post-load glucose (available upon request from NS).

In people who had no history of diabetes and fasting glucose <7.0 mmol/l at baseline, adjusted HR for CHD was 0.95 (0.89–1.01) per 1 mmol/l higher fasting glucose and 1.03 (1.01–1.05) per 1 mmol/l higher 1-h post-load glucose. Similar findings were observed in analyses that: explored HRs in a range of clinically relevant subgroups (Figure S3); assessed HRs in 5-y intervals of follow-up (available upon request); or excluded people with post-load glucose levels ≥11.1 mmol/l (available upon request). Compared with individuals with fasting glucose <5.6 mmol/l, adjusted HRs for CHD were: 1.27 (0.96–1.68) with fasting glucose levels 6.1–7.0 mmol/l and 1.08 (0.87–1.33) with fasting glucose levels 5.6–6.1 mmol/l (i.e., corresponding to categories of fasting glucose concentration used to define impaired fasting glucose).

**Discussion**

The current data indicate that fasting and post-load glucose and HbA1c each have reasonably high degrees of long-term within-person reproducibility (i.e., broadly comparable to such reproducibility values for total cholesterol and systolic blood pressure).
The current meta-analysis of data from population-based Western prospective studies involving a total of >300,000 people (~17,000 incident CHD cases) indicate that fasting glucose concentration is modestly associated with CHD risk in people without diabetes, i.e., RR for CHD was about 1.06 per 1 mmol/l higher fasting glucose. Furthermore, in the Reykjavik prospective study, RRs were generally modest and nonsignificant across glucose values below the diabetes definition (i.e., fasting glucose <7 mmol/l). We observed similar results in relation to post-load glucose. The current findings contrast with those from some smaller previous studies, which have suggested that glucose values are log-linearly and more strongly associated with CHD risk (including at glucose values lower than those defining diabetes). Because previous epidemiological estimates have influenced scientific guideline statements [40], clinical risk assessment strategies [41], burden of disease estimates [42], and public health policy recommendations [43], it may be helpful to review such efforts in the light of the current updated epidemiological evidence. Careful consideration may also need to be given to the design and interpretation of trials of CHD prevention using glucose-lowering agents in people without diabetes, as the current findings suggest that trial sample sizes required may be larger than previously anticipated [44-47].

In contrast with findings for glucose concentration, the current meta-analysis has indicated a RR for CHD of 1.20 per 1% higher HbA1c in people without diabetes. Although RRs for CHD appear stronger with HbA1c than those with glucose concentration, this possibility requires careful interpretation because: (1) the comparison is an indirect one (i.e., fasting glucose and HbA1c measurements were typically not made in the same participants) and (2) fewer than one-fifth as many incident CHD cases have been reported with HbA1c, as with glucose concentration (so associations with HbA1c cannot be quantified as reliably as those with glucose levels). Nevertheless, because the current data suggest that fasting glucose and HbA1c have similar levels of within-person variability over several years, such variability seems unlikely to account for differences seen in RRs with different measures of dysglycaemia. It remains uncertain whether HbA1c is a more informative measure of dysglycaemia than are fasting or post-load glucose levels, more accurately reflects processes relevant to vascular damage in response to glycation, or some combination of these possibilities [2,48].

The strengths and potential limitations of this study merit consideration. For fasting glucose, the Reykjavik study involves more incident CHD cases than in any previous prospective study. It identified participants in population registers, achieved high response and follow-up rates, and entailed robust ascertainment of incident MI and fatal CHD. We have demonstrated the validity of the glucose measurements in capillary whole blood samples by showing: the expected strong associations of fasting glucose levels with CHD in people with values ≥7.0 mmol/l; long-term within-person consistency of glucose concentration comparable to that for systolic blood pressure and total cholesterol concentration; and similar findings as in previous studies that used plasma or serum. For post-load glucose, RRs in the Reykjavik study (involving assessment 1 h after ingestion of a 50 g glucose load) were very similar to RRs in studies involving assessment 2 h after ingestion of a 75 g glucose load.

As findings in the Reykjavik study were reinforced by a meta-analysis of tabular data from 26 other long-term prospective studies located in ten Western countries, it increases the likelihood that these results can be extrapolated, at least to other Western populations. Although our review focused only on Western cohorts to reduce heterogeneity, it may be relevant to note that the largest available prospective study in East Asia (~3,100 incident MI outcomes) has reported similar findings to those described here, concluding that fasting glucose concentration has no clear association with MI risk below the diabetes definition [49]. Our meta-analysis included >85% of the relevant data identified by the systematic review (and a literature-based sensitivity analyses of noncontributing studies yielded broadly similar findings). Although we noted heterogeneity, it was not explained by the characteristics recorded here. Because some previous reviews did not consistently exclude people with diabetes at baseline [3,4] or involved only fatal CHD [5], it is difficult to compare their RRs directly with the RRs observed here. A more detailed consideration of available prospective studies, perhaps on the basis of combination of individual participant data, will enable more reliable analyses under a broader range of circumstances and a more detailed investigation of potential sources of diversity.

Conclusions

In people without diabetes, fasting and post-load glucose levels were modestly associated with CHD risk. Associations of HbA1c with CHD risk in such people appeared somewhat stronger. Scientific guidelines, policies, and trial designs premised on the existence of strong, log-linear associations of fasting and post-load glucose concentration with CHD risk may benefit from review in light of these epidemiological findings.

Supporting Information

Figure S1 Risk of coronary heart disease across tenths of baseline fasting glucose in the Reykjavik Study, adjusted for age and sex only.
Found at: doi:10.1371/journal.pmed.1000278.s001 (0.04 MB DOC)

Figure S2 Risk of coronary heart disease across tenths of usual fasting glucose in the Reykjavik Study.
Found at: doi:10.1371/journal.pmed.1000278.s002 (0.04 MB DOC)

Figure S3 Hazard ratios for coronary heart disease per 1 mmol/l higher fasting and 1-h post-load glucose concentration in individuals without diabetes in the Reykjavik Study, grouped by several characteristics.
Found at: doi:10.1371/journal.pmed.1000278.s003 (0.04 MB DOC)

Table S1 Copy of form used to seek tabular data for the updated meta-analysis in the present report.
Found at: doi:10.1371/journal.pmed.1000278.s004 (0.04 MB DOC)

Table S2 Baseline characteristics of study participants at the initial examination in the Reykjavik Study.
Found at: doi:10.1371/journal.pmed.1000278.s005 (0.04 MB DOC)
Table S3  Baseline correlates of fasting blood glucose and 1-h post-load glucose in participants without diabetes at the initial examination in the Reykjavik Study.
Found at: doi:10.1371/journal.pmed.1000278.s006 (0.04 MB DOC)

Table S4 Characteristics of prospective studies in Western populations of markers of dysglycaemia and coronary heart disease risk in individuals without diabetes included in the current analyses.
Found at: doi:10.1371/journal.pmed.1000278.s007 (0.10 MB DOC)

Text S1 Appendix.
Found at: doi:10.1371/journal.pmed.1000278.s008 (0.10 MB DOC)

Note Added in Proof
Investigators of an additional study of fasting glucose concentration and CHD [50], involving a further 6,447 participants and 862 incident CHD cases, provided tabular data while this article was in proof. After addition of these data to the meta-analysis, the combined adjusted relative risk for CHD was 1.05 (1.00–1.10) per 1 mmol/l higher fasting glucose concentration (24 cohorts, 11,670 cases, 261,618 participants).

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References

1. Goldstein DE, Little RR, Lormer RA, Malone JL, Nathan DM, et al. (2003) Tests of glycemia in diabetes. Diabetes Care 26: 1683–8.
2. Beckman JA, Creager MA, Libby P (2002) Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 287: 2570–81.
3. Cintiho M, Gerstein HC, Wang Y, Yusuf S (1999) The relationship between glucose and incident cardiovascular events. A meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 22: 233–40.
4. Levin EB, Song Y, Ford ES, Liu S (2004) Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med 164: 2174–55.
5. DECODE Study Group, the European Diabetes Epidemiology Group (2001) Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 161: 397–405.
6. Helfand M, Buckley DI, Freeman M, Fu R, Rogers K, et al. (2009) Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med 141: 496–507.
7. Ulmer H, Kelleher C, Diem G, Concim H (2004) Why Eve is not Adam: prospective follow-up in 149650 women and men of cholesterol and other risk factors related to cardiovascular and all-cause mortality. J Women Health (Larchmt) 13: 41–53.
8. Eberly LE, Pirnes R, Cohen JD, Vazquez G, Zhi X, et al. (2006) Metabolic syndrome: risk factor distribution and 18-year mortality in the multiple risk factor intervention trial. Diabetes Care 29: 123–30.
9. Smith NL, Barzilai H, Shaffer D, Savage PJ, Heckbert SR, et al. (2002) Fasting and 2-hour postchallenge serum glucose measures and risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study. Arch Intern Med 162: 1163–70.
10. Saydah SH, Mirtz M, Sung J, Varas C, Gause D, et al. (2001) Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. Diabetes Care 24: 1397–402.
11. Cruz-Vidal M, Garcia-Palmieri MR, Costas R, Jr., Sorlie PD, Haffner SM (1983) Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 26: 1250–7.
12. Selvin E, Cored J, Golden SH, Brancati FL, Folsom AR, et al. (2005) Glycemic control and coronary heart disease risk in persons with and without diabetes: the atherosclerosis risk in communities study. Arch Intern Med 165: 1910–6.
13. Bjornholt JV, Eriksen G, Aaser S, Sandvik L, Nitter-Hauge S, et al. (1999) Fasting blood glucose: an underestimated risk factor for cardiovascular death. Results from a 22-year follow-up of healthy nondiabetic men. Diabetes Care 22: 45–9.
14. Rodriguez BL, Lau N, Burchfield CM, Abbott RD, Sharp DS, et al. (1999) Glucose intolerance and 23-year risk of coronary heart disease and total mortality: the Honolulu Heart Program. Diabetes Care 22: 1262–5.
15. Pyorala M, Miettinen H, Halonen P, Haakon P, Pyorala K (2000) Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. Arterioscler Thromb Vasc Biol 20: 38–44.
16. Marin A, Medrano MJ, Gonzalez J, Pintado H, Compared V, et al. (2006) Risk of ischaemic heart disease and acute myocardial infarction in a Spanish population: observational prospective study in a primary-care setting. BMJ Public Health 6: 38.
17. Meigs JB, Nathon DM, D’Agostino RB, Sr, Wilson PW; Framingham Offspring Study. (2002) Fasting and postchallenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. Diabetes Care 25: 1451–50.
18. Lavender DA, Smith GD, Ehrenberg S (2006) Does the new International Diabetes Federation definition of the metabolic syndrome predict CHD any more strongly than older definitions? Findings from the British Women’s Heart and Health Study. Diabetologia 49: 41–8.
19. Adams RJ, Appleton SL, Hill CI, Wilson DH, Taylor AW, et al. (2009) Independent association of Hba1c and incident cardiovascular disease in people without diabetes. Obesity (Silver Spring) 17: 559–63.
20. Riazi A, Zimmet PZ, Wellenius GA, Jolley D, Magliano DJ, et al. (2007) Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation 116: 151–7.
21. Brunner EJ, Shipley MJ, Witter DR, Fuller JH, Marmot MG. (2006) Relation between blood glucose and coronary mortality over 33 years in the Whitehall Study. Diabetes Care 29: 26–31.
22. Orencia AJ, Davulis MI, Dyer AR, Walsh M, Greenland P, et al. (1997) One-hour postload plasma glucose and risks of fatal coronary heart disease and stroke among nondiabetic men and women: the Chicago Heart Association Detection Project in Industry (CHADI) Study. J Clin Epidemiol 50: 1369–76.
23. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, et al. (2004) Association of haemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. Ann Intern Med 141: 413–20.
24. Jonsdottr IS, Sigfusson N, Gudnason V, Sigvaldason H, Thorgerisson G (2002) Diabetes, blood pressure, diabetes, and smoking confer equal risk of myocardial infarction in women as in men? The Reykjavik Study. J Cardiovasc Risk 9: 67–76.
25. Hoffman WS (1973) Rapid photoelectric method for the determination of glucose in blood and urine. J Biol Chem 248: 51–4.
26. Easton DF, Post J, Babiker AG (1991) Fasting absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. Stat Med 10: 1025–35.
27. Grandits GA, Shipley M, Lewington S, Youngman L, Collins R, et al. (1999) Underestimation of risk associations due to regression dilation in long-term follow-up of prospective studies. Am J Epidemiol 150: 341–353.
28. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2002) Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 25: 567–64.
29. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557–60.
38. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629–34.
39. WHO consultation report. Definition, diagnosis and classification of diabetes mellitus and its complications. WHO/NCD/NCS/91.2.
40. Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC), European Association for the Study of Diabetes (EASD). (2007) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. Eur Heart J 28: 88–136.
41. Kahn R, Buse J, Ferrannini E, Stern M (2005) The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 28: 2289–304.
42. Danaei G, Lawes CM, Vander Hoorn S, Murray CJ, Ezzati M (2006) Global and regional mortality from ischaemic heart disease and stroke attributable to higher-than-optimum blood glucose concentration: comparative risk assessment. Lancet 368: 1651–9.
43. Avendano M, Mackenbach JP (2006) Blood glucose levels: facing a global crisis. Lancet 368: 1631–2.
44. Origin Trial Investigators, Gerstein H, Yusuf S, Riddle MC, Ryden L, et al. (2008) Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). Am Heart J 155: 26–32.
45. Holman RR (2007) A new era in the secondary prevention of CVD in prediabetes - the Acarbose Cardiovascular Evaluation (ACE) trial. Diab Vasc Dis Res 4 (Suppl 1): S40.
46. DREAM Trial Investigators, Dagenais GR, Gerstein HC, Holman R, Budaj A, et al. (2006) Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. Diabetes Care 31: 1007–1014.
47. The NAVIGATOR Study Group, Holman RR, Haffner SM, McMurray JJ, et al. (2010) Effect of Nateglinide on the Incidence of Diabetes and Cardiovascular Events. N Engl J Med 362: 1463–1476.
48. Khaw KT, Wareham N (2006) Glycated haemoglobin as a marker of cardiovascular risk. Curr Opin Lipidol 17: 637–43.
49. Sung J, Song YM, Elahim S, Lawlor DA (2009) Fasting blood glucose and the risk of stroke and myocardial infarction. Circulation 119: 812–9.
50. Preiss D, Welsh P, Murray HM, Shepherd J, Packard C, et al. (2010) Fasting plasma glucose in non-diabetic participants and the risk for incident cardiovascular events, diabetes, and mortality: results from WOSCOPS 15-year follow-up. Eur Heart J. Epub ahead of print. doi:10.1093/eurheartj/ehq095.
Editors’ Summary

Background. Among people diagnosed with type 2 diabetes mellitus (the commonest type of diabetes worldwide), poor management or lack of appropriate treatment can lead to long-term complications resulting from persistently high sugar levels in the blood. The long-term complications of type 2 diabetes are generally divided into two main groups: microvascular problems (such as nerve damage, kidney disease, and eye disorders), and macrovascular disease (such as heart disease, strokes, and peripheral vascular disease). A major goal of diabetes treatment is to keep glucose control as normal as possible through diet, weight control, exercise, and pharmacological treatments. However, it is unclear whether the link between high blood sugar and macrovascular disease (principally heart disease and strokes) also holds for people who have slightly higher than normal blood sugar levels, but in whom this level does not reach the diabetic threshold. Some previous research studies have suggested that a continuous relationship exists between blood sugar level and the risk of heart disease across the spectrum, i.e., below the diabetic threshold as well as above it. If such a relationship were confirmed this might have important implications for the management of high blood sugar levels even among people who would not normally meet the usual definition for a diagnosis of diabetes (the “diabetic threshold”).

Why Was This Study Done? Studies which examine the risk of serious, but relatively common, outcomes (such as a nonfatal heart attack or fatal heart disease), often suffer from insufficient statistical power: a large number of participants need to be recruited, and followed up over a long time, to find out whether certain factors measured at baseline (e.g., fasting glucose) are indeed associated with a particular outcome (e.g., heart attack) or not during follow up. Given the inconclusive nature of some previous studies in this area, the researchers who carried out this work wanted to gather evidence from a large prospective cohort, and a reappraisal of all existing evidence, in relation to the possible link between high blood sugar and risk of heart disease in people without diabetes.

What Did the Researchers Do and Find? In this study, the researchers report results from a prospective population-based study (in which participants are followed forward in time) from Reykjavik, Iceland. In the study, men and women without history of heart disease aged between 31 and 57 in 1966 were first invited to join the cohort, and were followed forward in time using national registries that recorded deaths (and causes of death), and incidence of heart disease. A total of 8,888 male and 9,681 female participants were recruited. At baseline, laboratory measurements were taken to record blood sugar levels using two different methods: fasting blood glucose and post-load glucose. Among the group of participants, 4,664 people were recorded as having either a nonfatal heart attack or fatal heart disease, during approximately 23 years of follow-up. In addition, the researchers attempted to identify from the published medical literature previous prospective studies conducted in Western populations that had looked at the association between blood sugar levels and risk of coronary heart disease. They requested, and obtained, re-analyses of data conducted in accordance with a common protocol for most of the identified studies and then analysed these, together with the results of the Reykjavik cohort, to produce a summary estimate (meta-analysis) of the association between blood sugar levels and risk of coronary heart disease in people without diabetes.

In the Reykjavik cohort, the researchers confirmed an increased risk of coronary heart disease among individuals with blood sugar above the diabetic threshold, as compared to those below it. However, when they looked at blood sugar in people below the diabetic threshold, they found no evidence that higher levels were strongly linked with greater risk of coronary heart disease. This held for both methods of measuring blood sugar levels (fasting and post-load). In the meta-analysis, the researchers obtained data for 27 different studies, comprising 303,961 participants and 16,982 cases of heart disease. In this meta-analysis, very small increases in risk of heart disease were found with higher levels of blood sugar, when measured using fasting blood glucose or post-load glucose. However, studies using glycated haemoglobin (a measure of average sugar levels over the past 1–3 months or so) found this measure to be associated with a somewhat higher risk of heart disease.

What Do these Findings Mean? In this prospective cohort and wider meta-analysis, the researchers did not find evidence of a strong or continuous association between blood sugar levels and risk of heart disease amongst people without diabetes. The prospective study, and analysis of other cohorts, was large, but only looked at participants of European decent, so it is not clear whether the findings will also hold for non-European groups.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1000278.

- Information is available from the US National Diabetes Information Clearinghouse about diabetes, heart disease, and stroke
- Centers for Disease Control provides information for the public and professionals about diabetes on their diabetes minisite
- Medline Plus encyclopedia has an entry about coronary heart disease