Fasting plasma glucose in non-diabetic participants and the risk for incident cardiovascular events, diabetes, and mortality: results from WOSCOPS 15-year follow-up†

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Aims
The evidence base for fasting plasma glucose (FPG) in the non-diabetic range as a risk factor for cardiovascular disease (CVD) is inconclusive. We investigated this question in the West of Scotland Coronary Prevention Study (WOSCOPS).

Methods and results
In WOSCOPS, we related FPG in 6447 men (mean age 55 years) with hypercholesterolaemia, but no history of CVD or diabetes, to the risk of cardiovascular events and mortality over 14.7 years of follow-up; 2381 non-fatal/fatal cardiovascular events and 1244 deaths occurred. Participants were divided into fifths of baseline FPG, Q1 (<4.3 mmol/L) to Q5 (>5.1–6.9 mmol/L). Q2 was designated the referent based on previous studies which have suggested a J-shaped relationship between FPG and CVD. Compared with Q2 (4.3–4.6 mmol/L), men in Q5 had no elevated risk for cardiovascular events [hazard ratio (HR) 0.95 (0.83–1.08)], or all-cause mortality [HR 0.96 (0.80–1.15)] in fully adjusted analyses despite a significant risk for incident diabetes [HR 22.05 (10.75–45.22)]. After further dividing Q5 into fifths, Q5a–e, individuals in Q5e (FPG 5.8–6.9 mmol/L) were also not at increased risk of cardiovascular events [HR 1.05 (0.82–1.35)] or other endpoints compared with Q2. All results were similar using Q1 as the referent.

Conclusion
Elevations in FPG in the non-diabetic range were not associated with long-term risk of cardiovascular events in middle-aged men in WOSCOPS. These data suggest that the current FPG cutoff for diagnosing diabetes also appropriately identifies western men at risk of CVD.

Keywords
Cardiovascular disease • Impaired fasting glycaemia • Diabetes mellitus • Glucose

Introduction
Diabetes mellitus is an established independent risk factor for cardiovascular events and cardiovascular death.1 Reports have suggested that elevated fasting plasma glucose (FPG) levels within the non-diabetic glycaemic range are associated with an increased risk of cardiovascular disease (CVD).2,3 The quality of the older data on which these conclusions are based is variable; methodological problems include the inclusion of subjects with FPG levels within the diabetic range. In a meta-analysis of 14 studies,2 a risk ratio of 1.27 for cardiovascular events in the highest category of FPG compared with the lowest category was reported. However, 7 of the 14 studies included participants with fasting glucose ≥7.0 mmol/L, and, of the remaining seven...
studies, four found no association between fasting glucose and CVD.\textsuperscript{2} When diabetic individuals are included, as in that meta-analysis,\textsuperscript{3} the association of FPG with the risk of CVD is not linear (the authors suggested a threshold effect at 5.6 mmol/L), and therefore reporting of continuous risk associations is potentially misleading. More recent data have shown no association between FPG and coronary heart disease (CHD) within the non-diabetic range in Korean men\textsuperscript{4} and in British women.\textsuperscript{5} On the other hand, a weak association between impaired fasting glycaemia (IFG) and CVD was observed in a Chinese population,\textsuperscript{6} and a possible J-shaped relationship between FPG and CVD mortality was observed in the AusDiab\textsuperscript{2} and DECODE studies.\textsuperscript{7} In DECODE,\textsuperscript{8} IFG was associated with higher rates of all-cause mortality in men [hazard ratio (HR) 1.21] but not in women (HR 1.09) in age-adjusted analyses.

To help clarify the disparate literature, we related baseline FPG levels to the risk of incident CVD events, all-cause death, and the development of diabetes in the West of Scotland Coronary Prevention Study (WOSCOPS), for which 15-year follow-up data of CVD events are now available.\textsuperscript{9}

**Methods**

**WOSCOPS participants**

The design of WOSCOPS has been reported elsewhere.\textsuperscript{10,11} Briefly, 6595 moderately hypercholesterolaemic men (serum LDL cholesterol 4.5–6.0 mmol/L and triglycerides < 6.0 mmol/L) with no history of myocardial infarction (MI) were randomized to pravastatin 40 mg daily or placebo and followed initially for an average of 4.9 years, with an additional follow-up to 15 years.\textsuperscript{10} All subjects provided written informed consent, and ethical approval was obtained. Men attended the screening clinic (before randomization to pravastatin or placebo) fasted and had plasma samples taken. Fasting glucose measurements were carried out in quality-controlled National Health Service (NHS) routine laboratories, and subsequent FPG measurements were made throughout the study at six monthly visits. A range of other physical and biochemical CVD risk factors and other demographic variables was assessed at baseline.\textsuperscript{11}

To allow comparison of the different relationships between FPG and future CVD and diabetes, we related baseline FPG to future development of both CVD (data available up to 15 years) and diabetes (data available up to 5 years). Finally, we calculated the risk of various CVD endpoints and all-cause death in those with baseline diabetes and also those who had developed diabetes during WOSCOPS.

**Diagnoses of events**

Specific diseases and events examined in the current analysis were as follows.

- **Diabetes mellitus.** Known baseline diabetes was defined by physician-reporting of diabetes. Newly diagnosed baseline diabetes was defined as FPG ≥ 7.0 mmol/L. Incident diabetes after baseline was defined as two subsequent FPG measurements ≥ 7.0 mmol/L or commencement of hypoglycaemic agents during the study.

- **Cardiovascular endpoints and all-cause mortality.** As detailed previously,\textsuperscript{10} follow-up of clinical CVD events and mortality was based on linkage of records held by the NHS Scotland, a technique already shown to demonstrate close correlation to event adjudication by end-point committee.\textsuperscript{12} Personal identifiers for study participants were electronically linked to hospital discharge records (Scottish Morbidity Record 01) and General Register Office death records (held by the Information and Statistical Division of NHS Scotland) by means of established record-linkage methods. Data on outcome events were extracted from the databases with the use of appropriate ‘International Classification of Diseases’ codes (versions 9 and 10). Approval for record linkage was given by the Privacy Advisory Committee at the Information and Statistics Division of NHS Scotland. Cardiovascular events were defined as:

  - (i) CVD events: a composite of non-fatal CVD events and fatal CVD events (ICD 10: I00–I99);
  - (ii) CHD events: a composite of non-fatal CHD events and CHD death (ICD 10: I10–I15);
  - (iii) stroke: a composite of non-fatal and fatal stroke (ICD 10: I60–I69);
  - (iv) CHD death;
  - (v) all-cause mortality.

**Statistics**

To examine the potential relationships between non-diabetic fasting glucose and future CVD events, CHD death, all-cause death, and new-onset diabetes, we divided FPG for baseline non-diabetics into fifths (Q1–Q5), thereby allowing comparison of time to first event of interest by Cox proportional hazards models with Q2 as referent. We selected Q2 as the referent based on previous analyses suggesting a J-shaped relationship between FPG and CVD mortality and used Q1 as a referent in sensitivity analyses. The HRs were adjusted for treatment and age in a minimally adjusted model and additionally for the following baseline covariates [treatment, age, cholesterol (HDL and LDL), triglycerides, BMI, smoking status (current and ex), BP (systolic and diastolic), hypertension, nitrates, angina, social deprivation score (DEPCAT), specific medications at baseline (aspirin, ACE-inhibitors, β-blockers, calcium channel blockers, diuretics, other antihypertensives)] in a fully adjusted model. Given possible weighting of events by FPG close to the diabetes threshold of 7.0 mmol/L, the uppermost FPG quintile was further divided into fifths (Q5a–Q5e) for more detailed analysis. Cardiovascular disease risk was assessed in those with baseline IFG [using two definitions: the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII)\textsuperscript{13} (FPG 6.1–6.9 mmol/L) and American Diabetes Association (ADA)\textsuperscript{14} (FPG 5.6–6.9 mmol/L)], in baseline diabetics and in those who had developed diabetes during the 4.9 years of WOSCOPS. Results are reported as number (percentage) of events, HR [95% confidence interval (CI)], and corresponding P-values; P-values were two-sided and P < 0.05 was considered statistically significant. The validity of the proportional hazards assumption was assessed by testing the significance of interaction between glucose and the logarithm of time as a time-dependent covariate. All analyses were carried out using the statistical software SAS (version 9.1, SAS Institute, Cary, NC, USA).

**Results**

**Cardiovascular disease events and all-cause mortality**

Data were available for 6447 participants with no baseline diabetes and with fasting glucose < 7.0 mmol/L. Baseline characteristics, split according to quintiles of fasting glucose, are provided in Table 1. Over 15 years of follow-up, the number of clinical events was: 2381 CVD events, 1474 CHD events, 405 strokes, 361 CHD deaths, and 1244 all-cause deaths.
Risk of cardiovascular disease and mortality in different glycaemic categories

There was no significant difference in the association of FPG with the risk of endpoints by pravastatin/placebo randomization: all CVD ($P = 0.29$), CHD ($P = 0.75$), stroke ($P = 0.99$), CHD death ($P = 0.72$), and all-cause mortality ($P = 0.69$). Hence, we pooled participants regardless of statin or placebo allocation, although treatment is included in all adjustment models. Results separated by treatment allocation are provided in the Supplementary material online tables.

Comparing the risk of cardiovascular and mortality endpoints across fifths of non-diabetic FPG by HR relative to Q2, none of the other quintiles (Q1, Q3–Q5) were at significantly increased or decreased risk of any adverse events in age- and treatment-adjusted analysis (Table 2). In this minimally adjusted model, Model 1, the HR for CVD events in Q5 relative to Q2 was 1.04 (95% CI 0.92–1.18). These findings were consistent for all endpoints after additionally adjusting for a range of potential confounders (Model 2). The highest fifth of FPG in the non-diabetic range (Q5: range $>5.1–6.9$ mmol/L) was subsequently further divided into fifths (Q5a–e: Table 3) and compared with Q2. None of the Q5a–e subgroups was at increased risk for any CVD endpoint or mortality relative to Q2 apart from all-cause mortality in Q5c. In age- and treatment-adjusted models, those in Q5e (FPG $>5.8–6.9$ mmol/L) were not at increased risk of CVD [HR 1.21 (95% CI 0.95–1.54)], and any trend towards an association was attenuated in the fully adjusted model [HR 1.05 (95% CI 0.82–1.35)]. All of these findings were consistently null when Q1 was used as the referent (data available on request).

Expressed as a continuous variable in fully adjusted models, HRs per 1 mmol/L higher glucose for CVD events [HR 0.95 (95% CI 0.88–1.04)], CHD events [HR 0.93 (95% CI 0.84–1.04)], strokes [HR 1.01 (95% CI 0.83–1.22)], and CHD death [HR 0.90 (95% CI 0.73–1.11)] were also not significant. However, as noted earlier, analysis of glucose in a continuous fashion implies that risk is linear, an assumption which is unproved.

We then estimated the risk of CVD and mortality endpoints in those who met two different criteria for IFG, namely that of NCEP ATP III (FPG 6.1–6.9 mmol/L) and the ADA (FPG 5.6–6.9 mmol/L) (Table 4). Using either criterion, the risk of CVD was not significantly elevated in those with IFG relative to those with lower fasting glucose in both minimally and fully adjusted models, though event numbers were low for stroke and CHD death.

In contrast, the risk of CVD events [HR 1.32 (95% CI 1.05–1.66)], CHD events [HR 1.46 (95% CI 1.10–1.92)], and all-cause mortality [HR 1.37 (95% CI 1.02–1.83)] was significantly increased in fully adjusted models in those with baseline diabetes ($n=148$) compared with all subjects without diabetes. Baseline diabetes was not associated with significantly different rates of CHD death [HR 1.47 (95% CI 0.88–2.45)] or stroke [HR 0.89 (95% CI 0.50–1.60)] though event numbers were lower.

Finally, the risk of CVD, CHD, and mortality endpoints was calculated from the end of the trial (at 5 years) over the subsequent 10 years in those ($n=138$) who had developed diabetes but not suffered any CHD or CVD events during WOSCOPS [note these are 138 patients from a total of 168 (see what follows) who developed diabetes during WOSCOPS; 30 were excluded from this analysis having suffered clinical events over the 5 years of the WOSCOPS trial]. Risk of CVD events [HR 1.29 (95% CI 0.98–1.69)], CHD events [HR 1.36 (95% CI 0.97–1.92)], stroke [HR 1.24 (95% CI 0.67–2.29)], CHD death [HR 1.57 (95% CI 0.75–3.32)], and all-cause mortality [HR 1.50 (95% CI 0.81–2.81)] were all also not significant.
WOSCOPS clearly demonstrated that FPG in the non-diabetes range was not associated with increased risk of CVD events, CHD death, or all-cause mortality. As expected, however, those with diabetes were at increased risk of these endpoints. Additionally, in contrast to the lack of association of FPG with CVD and mortality risk in those without diabetes, there was a substantial independent increase in the risk of new diabetes in those in the highest quintile of FPG. This clearly demonstrates that an elevated FPG level in the non-diabetic range is a powerful risk factor for future diabetes\textsuperscript{15} but not for CVD over 15 years of follow-up. WOSCOPS did not include measurements of either HbA1c or post-challenge glucose, potentially better markers of CVD risk.

Previous studies investigating potential associations between FPG <7.0 mmol/L and incident CVD events have produced variable results, and our findings are in disagreement with meta-analyses of earlier literature.\textsuperscript{3} However, many of the studies these are based on included patients who, by current definitions, had diabetes, and reporting was probably subject to some small study publication bias.\textsuperscript{3} More recently, a report in 652,901 Korean men, linked to national databases and followed for 10,954 events) was only clearly increased at FPG ≥4.3–4.6 mmol/L (HR 95% CI 1.03–1.21 relative to Q2, an association which remained in the fully adjusted model. Treatment allocation was not a relevant factor (see Supplementary material online table).

### Discussion

Analysis of the relationship between FPG and CVD events and all-cause mortality in hypercholesterolaemic western men in WOSCOPS clearly demonstrated that FPG in the non-diabetes range was not associated with increased risk of CVD events, CHD death, or all-cause mortality. As expected, however, those with diabetes were at increased risk of these endpoints. Additionally, in contrast to the lack of association of FPG with CVD and mortality risk in those without diabetes, there was a substantial independent increase in the risk of new diabetes in those in the highest quintile of FPG. This clearly demonstrates that an elevated FPG level in the non-diabetic range is a powerful risk factor for future diabetes\textsuperscript{15} but not for CVD over 15 years of follow-up. WOSCOPS did not include measurements of either HbA1c or post-challenge glucose, potentially better markers of CVD risk.

### Risk of incident diabetes in those without diabetes at baseline

There were 168 incident cases of diabetes over 5 years. We estimated the risk of new-onset diabetes over 5 years by quintiles of FPG and contrasted this with the risk of CVD events over 15 years (Figure 1). Despite higher FPG levels in the non-diabetic range not being associated with the risk of CVD events over 15 years, there was an extremely strong increase in the risk of diabetes in Q5 in age- and treatment-adjusted models [HR 26.5 (95% CI 12.9–54.17)] relative to Q2, an association which remained in the fully adjusted model [HR 22.05 (95% CI 10.75–45.22)]. Hazard ratio for developing diabetes in Q4 relative to Q2 was 22.7 (95% CI 9.59–54.42) in the fully adjusted model. Treatment allocation was not a relevant factor (see Supplementary material online table). Finally, both criteria for IFG, namely NCEP ATPIII [HR 23.2 (95% CI 15.7–34.3)] and ADA [HR 17.3 (95% CI 12.6–23.7)], demonstrated powerful risks for developing diabetes compared with lower glucose levels.
population addressing the proposed link between FPG and incident CVD risk. Moreover, WOSCOPS has one of the longest follow-ups of any studies.

It has long been known that the risk of CVD and mortality is higher in diabetic subjects than in those without diabetes. We confirm this observation in WOSCOPS, and our observed risk levels are of a similar magnitude to those recently reported in the Framingham model in individuals without diabetes. Data were available only for middle-aged men and not women, the Framingham cohort, and these results may not reflect the variation found in the general population; however, we observed no interaction of statin allocation on associations of FPG with the risk of endpoints, we adjusted for baseline randomization. There are many theoretical pathways for glucose (usually at very high concentrations) to mediate increased risk, such as inhibition of vascular smooth muscle cell apoptosis, stimulation of inflammation and oxidative stress, low-density lipoprotein oxidation, and increasing thrombotic potential. Furthermore, there has been intense interest in the potential use of intensive glucose-control therapy among people with diabetes to reduce CVD risk—trials have shown mixed efficacy and safety. It is possible both in people with diabetes and those free from it that HbA1C post-prandial glucose are better markers of CVD risk. Based on other literature, however, even if the risk associations for these markers are stronger than for FPG, they will be modest in strength, and at least one study has shown that adding HbA1C adds little in terms of CVD risk discrimination to the Framingham model in individuals without diabetes. This study has numerous strengths, including the use of a well-characterized middle-aged cohort without history of CVD or diabetes, a lengthy follow-up period allowing for study of any FPG legacy effect (at least up to 15 years), a standardized method for identifying clinical endpoints, and a large number of incident CVD events. Despite having only 4.9 years of follow-up for diabetes data, this was easily adequate to demonstrate a clear difference in the importance of elevated FPG for incident CVD and diabetes. Some weaknesses in the data must also be highlighted. Data were available only for middle-aged men and not women, and, although another group has recently reported broadly consistent results in cohorts of women, it is possible that CVD risk does increase in women at a lower FPG. The WOSCOPS data, this was easily adequate to demonstrate a clear difference in the importance of elevated FPG for incident CVD and diabetes. Some weaknesses in the data must also be highlighted. Data were available only for middle-aged men and not women, and, although another group has recently reported broadly consistent results in cohorts of women, it is possible that CVD risk does increase in women at a lower FPG. This study has numerous strengths, including the use of a well-characterized middle-aged cohort without history of CVD or diabetes, a lengthy follow-up period allowing for study of any FPG legacy effect (at least up to 15 years), a standardized method for identifying clinical endpoints, and a large number of incident CVD events. Despite having only 4.9 years of follow-up for diabetes data, this was easily adequate to demonstrate a clear difference in the importance of elevated FPG for incident CVD and diabetes. Some weaknesses in the data must also be highlighted. Data were available only for middle-aged men and not women, and, although another group has recently reported broadly consistent results in cohorts of women, it is possible that CVD risk does increase in women at a lower FPG.

### Table 3: Associations of fasting plasma glucose with cardiovascular disease by quintiles of Q5 relative to Q2 over 15 years

<table>
<thead>
<tr>
<th>Glucose (mmol/L)</th>
<th>Q2 &gt; 4.3–4.6 (n = 1657), referent</th>
<th>Q5a &gt; 5.1–5.2 (n = 223)</th>
<th>Q5b &gt; 5.2–5.4 (n = 354)</th>
<th>Q5c &gt; 5.4–5.5 (n = 95)</th>
<th>Q5d &gt; 5.5–5.8 (n = 226)</th>
<th>Q5e &gt; 5.8–6.9 (n = 178)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>CVD events</td>
<td>Events (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>589 (35.6)</td>
<td>90 (40.4)</td>
<td>124 (35.0)</td>
<td>41 (43.2)</td>
<td>76 (33.6)</td>
<td>73 (41.0)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.0</td>
<td>1.16 0.93–1.44</td>
<td>0.96 0.79–1.16</td>
<td>1.31 0.96–1.80</td>
<td>0.98 0.78–1.25</td>
<td>1.21 0.95–1.54</td>
</tr>
<tr>
<td>CHD events</td>
<td>Events (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>362 (21.8)</td>
<td>48 (21.5)</td>
<td>85 (24.0)</td>
<td>25 (26.3)</td>
<td>47 (20.8)</td>
<td>47 (26.4)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.0</td>
<td>0.98 0.73–1.33</td>
<td>1.08 0.85–1.37</td>
<td>1.30 0.86–1.94</td>
<td>1.00 0.74–1.36</td>
<td>1.25 0.92–1.69</td>
</tr>
<tr>
<td>Stroke</td>
<td>Events (%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>87 (5.2)</td>
<td>19 (8.5)</td>
<td>17 (4.8)</td>
<td>7 (7.4)</td>
<td>14 (6.2)</td>
<td>16 (9.0)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.0</td>
<td>1.57 0.96–2.58</td>
<td>0.84 0.50–1.42</td>
<td>1.49 0.69–3.23</td>
<td>1.20 0.68–2.11</td>
<td>1.65 0.97–2.81</td>
</tr>
<tr>
<td>CHD death</td>
<td>Events (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Model 1</td>
<td>95 (5.7)</td>
<td>9 (4.1)</td>
<td>19 (5.4)</td>
<td>4 (4.2)</td>
<td>11 (4.9)</td>
<td>15 (8.4)</td>
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<tr>
<td>Model 2</td>
<td>1.0</td>
<td>0.68 0.34–1.34</td>
<td>0.88 0.54–1.44</td>
<td>0.77 0.28–2.10</td>
<td>0.87 0.47–1.63</td>
<td>1.38 0.80–2.38</td>
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<tr>
<td>All-cause mortality</td>
<td>Events (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>301 (18.2)</td>
<td>41 (18.4)</td>
<td>59 (16.7)</td>
<td>25 (26.3)</td>
<td>47 (20.8)</td>
<td>43 (24.2)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.0</td>
<td>0.97 0.70–1.34</td>
<td>0.85 0.65–1.13</td>
<td>1.53 0.82–2.03</td>
<td>1.18 0.87–1.60</td>
<td>1.25 0.91–1.72</td>
</tr>
</tbody>
</table>

Model 1: adjusted for randomized treatment and age. Model 2: in addition, adjusted for BMI, smoking, BP, hypertension, cholesterol (HDL and LDL), triglycerides, nitrates use, history of angina, social deprivation score (DEPCAT), and various medications (aspirin, ACE-inhibitors, β-blockers, calcium channel blockers, diuretics, others). Multiply by 18 to convert glucose from mmol/L to mg/dL.

Q, quintile; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease.
between IFG (NCEP ATPIII criteria) and CVD events, as the number of participants with baseline IFG was small (n = 95).

Finally, although such an analysis may examine associations or lack thereof between glucose and CVD, causality cannot be proved or disproved. Regardless, it would appear that FPG in the non-diabetic range has either no relationship with incident CVD events or possibly a very weak association at the upper end which, if incorporated into CVD risk prediction algorithms, will not improve risk prediction.

In conclusion, the present data from WOSCOPS investigating any link between FPG levels in the non-diabetic range and incident CVD events suggest that no significant association exists in a white western male population. The current FPG cutoff for diagnosing diabetes therefore appropriately identifies western men at elevated risk of CVD.

Supplementary material

Supplementary material is available at European Heart Journal online.

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Conflict of interest: none declared.


