Enhanced Predictive Capability of a 1-Hour Oral Glucose Tolerance Test: A Prospective Population-Based Cohort Study

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OBJECTIVE
To examine whether the 1-h blood glucose measurement would be a more suitable screening tool for assessing the risk of diabetes and its complications than the 2-h measurement.

RESEARCH DESIGN AND METHODS
We conducted a prospective population-based cohort study of 4,867 men, randomly selected from prespecified birth cohorts between 1921 and 1949, who underwent an oral glucose tolerance test with blood glucose measurements at 0, 1, and 2 h. Subjects were followed for up to 39 years, with registry-based recording of events. Discriminative abilities of elevated 1-h (≥8.6 mmol/L) versus 2-h (≥7.8 mmol/L) glucose for predicting incident type 2 diabetes, vascular complications, and mortality were compared using Kaplan-Meier analysis, Cox proportional hazards regression, and net reclassification improvement.

RESULTS
Median age was 48 years (interquartile range [IQR] 48–49). During follow-up (median 33 years [IQR 24–37]), 636 (13%) developed type 2 diabetes. Elevated 1-h glucose was associated with incident diabetes (hazard ratio 3.40 [95% CI 2.90–3.98], P < 0.001) and provided better risk assessment than impaired glucose tolerance (Harrell concordance index 0.637 vs. 0.511, P < 0.001). Addition of a 1-h measurement in subjects stratified by fasting glucose provided greater net reclassification improvement than the addition of a 2-h measurement (0.214 vs. 0.016, respectively). Finally, the 1-h glucose was significantly associated with vascular complications and mortality.

CONCLUSIONS
The 1-h blood glucose level is a stronger predictor of future type 2 diabetes than the 2-h level and is associated with diabetes complications and mortality.

Type 2 diabetes is associated with significant morbidity and mortality and represents a major burden on health care systems worldwide (1,2). Several randomized clinical trials provide evidence that type 2 diabetes can be prevented or at least postponed with lifestyle modification and drug therapy, which makes identifying high-risk individuals particularly important (3–6). Traditionally, prediabetes has been defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) during a 2-h oral glucose tolerance test (OGTT), and interventional studies thus far have predominantly included subjects with IGT (7,8). However, not all subjects with prediabetes develop type 2 diabetes and Women’s Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA 2Cardiovascular and Metabolic Preventive Clinic, Department of Endocrinology, Centre for Individualized Medicine in Arterial Diseases, Odense University Hospital, Odense, Denmark 3Cardiology Section, Department of Internal Medicine, Holbaek Hospital, Holbaek, Denmark 4Center for Healthful Behavior Change, Department of Population Health, New York University School of Medicine, New York, NY 5Department of Clinical Sciences and Lund University Diabetes Centre, Lund University, Skåne University Hospital, Malmö, Sweden 6Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, and Diabetes Prevention Program, New York University Langone Health, New York University School of Medicine, New York, NY

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diabetes, and conversely, a significant number without prediabetes progress to
type 2 diabetes (9). Accumulating longitudi-
dinal evidence, pioneered in particular by
Abdul-Ghani and colleagues (10–18), sug-
suggests that the 1-h postload glucose level
during OGTT with a cutoff ≥8.6 mmol/L
(155 mg/dL) may be an early marker of
IGT and subsequent type 2 diabetes that
is potentially more useful than either fast-
ing or 2-h glucose levels. Furthermore,
from a pathophysiological perspective,
the 1-h glucose level is intriguing owing
to its seemingly strong correlation with
markers of both insulin secretion and sen-
sitivity (10,19,20). However, practical clin-
ical implications of using a 1-h glucose
measurement for prediction of type 2 di-
abetes and its associated complications
are less clear. Therefore, the aim of this
study was to examine whether the 1-h
blood glucose measurement would be a
more suitable screening tool for risk assess-
ment than the 2-h blood glucose alone.

RESEARCH DESIGN AND METHODS

All subjects were participants of the
Malmö Preventive Project (1974–1992),
a population-based case-finding program
with the objective of identifying high-risk
adults suitable for preventive measures.
Inhabitants of Malmö, Sweden, belonging
to prespecified birth cohorts (1921–1949)
were invited for an examination of cardio-
vascular risk factors, alcohol abuse, and
breast cancer. Progressively older men
were recruited later during the course of
the study. The participation rate was
71% (21–23). During the initial phase of
the study (9 September 1974 to 31 May
1978 [both inclusive]), 7,200 men were
consecutively included, of whom 5,364
underwent baseline OGTT. After exclu-
sion of subjects with a missing or invalid
1-h glucose measurement (7 of 5,364) or
known diabetes (100 of 5,364), and those
who emigrated (71 of 5,364), 5,182 indi-
viduals were left. Of these, a subset of
individuals at high risk—including those
with hypertension, hyperlipidemia, dia-
betes, and IGT, with the latter defined per
local standards as a 2-h blood glucose level
≥7.0 mmol/L (126 mg/dL) confirmed on a
separate day (315 of 5,182)—underwent
intervention. The intervention for IGT
comprised of dietary advice and in-
creased physical activity, most often in-
cluding frequent visits at an outpatient
clinic for up to 12 years after inclusion.
We also excluded these subjects; thus,
the final study population consisted of
4,867 men (Supplementary Fig. 1). In ad-
dition, 132 women recruited between
25 January 1977 and 6 January 1984 un-
derwent baseline OGTT. One was excluded
owing to known diabetes and 3 owing to
emigration, but none of them underwent
intervention, leaving a total of 128 female
subjects. The Malmö Preventive Project
was approved by the ethics committee
of Lund University and conducted in ac-
cordance with the Declaration of Helsinki.
All participants gave informed consent.

Baseline Variables

Participants used a self-administered
questionnaire to provide information on
lifestyle and medical history, including a
history of diabetes in first-degree relatives,
cardiovascular disease, and current medi-
cation. Prevalent diabetes was defined as
self-reported diabetes or according to the
Blood glucose and serum lipids were ob-
tained after an overnight (≥10 h) fast.
Blood glucose was analyzed using the glu-
cose oxidase (1974–1977) or the hexoki-
were analyzed using the local laboratory’s
standard methods. A 2-h OGTT was per-
formed by ingestion of 30 g glucose/m²
body surface area (DuBois formula), with
glucose levels determined at 0, 20, 40, 60, 90,
and 120 min (25). Analyses of postload
glucose levels were focused on measure-
ments at 1 h and 2 h.

Outcomes

We used national and local registries to
record clinical end points. Besides the
diagnosis itself, the date of diagnosis is also
coded in these registries. All events (type 2
diabetes, myocardial infarction, diabetic
retinopathy, and diabetes with peripheral
vascular complications, including ulcer)
were defined according to the relevant
ICD-7 to ICD-10 codes (Supplementary
Table 1). Reported validities in the Swed-
ish National Inpatient Register were high
for all diagnoses (26). Mortality follow-up
was based on the national registry on
causes of mortality at the Swedish Central
Bureau of Statistics. As follow-up was lim-
ited to 31 December 2013, the potential
minimum and maximum follow-up times
were 35 and 39 years, respectively.

Statistical Methods

Continuous variables are presented as
mean ± SD (normally distributed vari-
ables) or median (interquartile range
[IQR]) (non–normally distributed vari-
ables). Categorical variables are presented
as counts and corresponding percentages.
Kaplan-Meier analysis with the log-rank
test and Cox proportional hazards regres-
sion with Harrell concordance index (C in-
dex), assuming an uncensored policy for
handling ties, were used for assessment of
discriminative ability for postload glu-
cose measurements, including compari-
sions between predefined risk groups
(27). Hazard ratios (HRs) were reported unadjusted and adjusted for age, BMI,
IGF, triglycerides, and family history of
diabetes. Furthermore, the ability of 1-h
and 2-h postload glucose measurements
to enhance prognostication in addition to
fasting blood glucose was tested with cat-
egorical net reclassification improvement
(28). All glucose measurements were as-
sessed in a binary fashion, using the fol-
lowing cut points: IFG, fasting blood
glucose ≥5.6 mmol/L (100 mg/dL); ele-
vated 1-h blood glucose, ≥8.6 mmol/L
(155 mg/dL); and IGT, 2-h BG ≥7.8
mmol/L (140 mg/dL) (7,10). Analyses
were performed at 12 years and at max-
imal available follow-up, respectively.
This was because of the possibility of
the intervention among high-risk individ-
uals during the first 12 years after recruit-
ment affecting the study outcomes
because even though we attempted to
minimize the implications of the interven-
tion by excluding individuals who were
subjected to it, there may have been a
spillover effect to the control subjects,
given the population-based nature of
the study. Results obtained from the
women were reported separately. There-
fore, unless explicitly stated otherwise, all
analyses and conclusions were based on
the larger male population. The signifi-
cance level was 5% (two sided), and no
adjustments for multiple comparisons
were made, as the study was considered
exploratory. All analyses were performed
with IBM SPSS Statistics 23 (IBM, Armonk,
NY) and Stata/IC 15 (StataCorp, College
Station, TX).

RESULTS

Table 1 shows baseline anthropometric,
clinical, and laboratory characteristics of
the study participants. All 4,867 subjects
were male, with a median age of 48 years
(IQR 48–49; range 27–52), mean BMI 24.8 ±
3.1 kg/m², mean body surface area 1.93 ±
0.15 m², and mean total cholesterol level
5.8 ± 1.0 mmol/L (225 ± 40 mg/dL).
A history of a sedentary lifestyle (leisure time mostly spent on sedentary activities, including reading, television, and cinema) was reported in 2,757 (57%), and 655 (13%) had a first-degree relative with diabetes. Normal postload blood glucose levels (NGT/1h-normal) were found in 3,139 (65%), elevated glucose at 1 h only (NGT/1h-high) was found in 1,564 (32%), and IGT only (IGT/1h-normal) was found in in 32 (1%), and 132 (3%) had both elevated 1-h glucose and IGT (IGT/1h-high). Collectively, 1,696 (35%) individuals had elevated glucose at 1 h, and 164 (3%) had IGT. Glucose levels at 1 h and 2 h were moderately correlated (Pearson r = 0.332, P < 0.001) (Supplementary Fig. 2).

### Cumulative Events

Median follow-up time was 33 years (IQR 24–37). At 12 and 39 years, 65 (1%) and 636 (13%) individuals had been diagnosed with type 2 diabetes, corresponding to incidence densities of 1.2 and 4.8 per 1,000 person-years, respectively. Cumulative incidences were lowest in subjects with NGT/1h-normal, highest in subjects with IGT/1h-high, and greater in subjects with NGT/1h-high than in those with IGT/1h-normal (Table 2 and Supplementary Table 2).

### Hazard Risk

The Kaplan-Meier plot shows the unadjusted type 2 diabetes–free survival for risk categories based on postload blood glucose measurements (Fig. 1A and Supplementary Figs. 3 and 4). Congruent with the above, both crude and adjusted HRs for development of type 2 diabetes were significantly greater in risk categories including subjects with elevated 1-h blood glucose levels (Table 3 and Supplementary Table 3).

### Discriminative Ability

The presence of an elevated 1-h blood glucose level was associated with significantly greater discriminative ability than IGT based on 2-h blood glucose at both 12 years (C index 0.698 vs. 0.553, P < 0.001) and 39 years (C index 0.637 vs. 0.511, P < 0.001). Additionally, the presence of IFG or elevated 1-h blood glucose was associated with a greater risk of type 2 diabetes than IFG or IGT at 12 years (HR 7.22 [95% CI 3.99–13.26], P < 0.001, C index 0.720, vs. HR 4.64 [95% CI 2.69–7.99], P < 0.001, C index 0.600; P for difference <0.001) and 39 years (HR 3.31 [95% CI 2.82–3.88], P < 0.001, C index 0.636, vs. HR 2.28 [95% CI 1.83–2.84], P < 0.001, C index 0.537; P for difference < 0.001).

### Table 1—Baseline characteristics of the study population, stratified according to glycemic category

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>NGT/1h-normal</th>
<th>NGT/1h-high</th>
<th>IGT/1h-normal</th>
<th>IGT/1h-high</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>4,867</td>
<td>3,139 (65)</td>
<td>1,564 (32)</td>
<td>32 (1)</td>
<td>132 (3)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>48 (48–49)</td>
<td>48 (48–49)</td>
<td>48 (48–49)</td>
<td>48 (47–49)</td>
<td>48 (48–49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Active smoking</td>
<td>2,582 (53)</td>
<td>1,583 (50)</td>
<td>934 (60)</td>
<td>8 (25)</td>
<td>57 (43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>655 (13)</td>
<td>375 (12)</td>
<td>254 (16)</td>
<td>6 (19)</td>
<td>20 (15)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>2,757 (57)</td>
<td>1,740 (55)</td>
<td>914 (58)</td>
<td>20 (63)</td>
<td>83 (63)</td>
<td>0.09</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8 ± 3.1</td>
<td>24.6 ± 3.0</td>
<td>25.1 ± 3.3</td>
<td>25.7 ± 3.6</td>
<td>25.7 ± 3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>130 ± 16</td>
<td>128 ± 14</td>
<td>134 ± 17</td>
<td>133 ± 19</td>
<td>143 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>88 ± 10</td>
<td>87 ± 10</td>
<td>90 ± 10</td>
<td>90 ± 14</td>
<td>94 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/L [mg/dL]</td>
<td>4.6 ± 0.5 (83 ± 10)</td>
<td>4.5 ± 0.5 (81 ± 9)</td>
<td>4.8 ± 0.5 (87 ± 10)</td>
<td>4.8 ± 0.6 (87 ± 11)</td>
<td>5.0 ± 0.6 (90 ± 11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>20-min blood glucose, mmol/L [mg/dL]</td>
<td>7.6 ± 1.4 (137 ± 25)</td>
<td>7.3 ± 1.3 (131 ± 23)</td>
<td>8.2 ± 1.3 (148 ± 24)</td>
<td>6.7 ± 1.2 (121 ± 22)</td>
<td>7.9 ± 1.4 (142 ± 26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40-min blood glucose, mmol/L [mg/dL]</td>
<td>9.0 ± 1.8 (162 ± 32)</td>
<td>8.2 ± 1.3 (147 ± 24)</td>
<td>10.5 ± 1.5 (188 ± 27)</td>
<td>8.0 ± 1.2 (144 ± 22)</td>
<td>10.5 ± 1.6 (189 ± 28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-h blood glucose, mmol/L [mg/dL]</td>
<td>8.0 ± 1.9 (143 ± 35)</td>
<td>6.8 ± 1.1 (123 ± 20)</td>
<td>10.0 ± 1.2 (180 ± 22)</td>
<td>7.4 ± 0.7 (133 ± 13)</td>
<td>11.0 ± 1.6 (198 ± 28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-h blood glucose, mmol/L [mg/dL]</td>
<td>5.2 ± 1.3 (94 ± 23)</td>
<td>4.9 ± 1.1 (89 ± 20)</td>
<td>5.4 ± 1.2 (98 ± 21)</td>
<td>8.1 ± 0.3 (146 ± 6)</td>
<td>8.6 ± 0.7 (155 ± 12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L [mg/dL]</td>
<td>5.8 ± 1.0 (225 ± 40)</td>
<td>5.8 ± 1.0 (223 ± 39)</td>
<td>5.9 ± 1.0 (228 ± 40)</td>
<td>5.7 ± 1.0 (222 ± 40)</td>
<td>6.1 ± 1.0 (238 ± 39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L [mg/dL]</td>
<td>1.4 (1.0–1.8) [121 (92–163)]</td>
<td>1.3 (1.0–1.7) [116 (89–152)]</td>
<td>1.5 (1.1–2.1) [133 (97–182)]</td>
<td>1.4 (1.1–2.3) [120 (99–205)]</td>
<td>1.6 (1.1–2.1) [140 (101–184)]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± SD (normally distributed variables: BMI, blood pressure, blood glucose, and total cholesterol) or median (IQR) (non-normally distributed variables: age and triglycerides). Data for the study population (first row) and categorical variables (active smoking, family history of diabetes, and sedentary lifestyle) are presented as counts and corresponding percentages. aKruskal-Wallis rank test. bPearson χ² test. cOne-way ANOVA.

### Table 2—Cumulative incidence and incidence density of type 2 diabetes, stratified according to glycemic category

<table>
<thead>
<tr>
<th>Study population, n (%)</th>
<th>Total</th>
<th>NGT/1h-normal</th>
<th>NGT/1h-high</th>
<th>IGT/1h-normal</th>
<th>IGT/1h-high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes cumulative incidence, n (%)</td>
<td>4,867</td>
<td>3,139 (65)</td>
<td>1,564 (32)</td>
<td>32 (1)</td>
<td>132 (3)</td>
</tr>
<tr>
<td>12 years</td>
<td>65 (1)</td>
<td>17 (0.5)</td>
<td>39 (2)</td>
<td>0</td>
<td>9 (7)</td>
</tr>
<tr>
<td>39 years</td>
<td>636 (13)</td>
<td>259 (8)</td>
<td>343 (22)</td>
<td>4 (13)</td>
<td>30 (23)</td>
</tr>
<tr>
<td>Type 2 diabetes incidence, per 1,000 person-years</td>
<td>12 years</td>
<td>1.2</td>
<td>0.5</td>
<td>2.2</td>
<td>0</td>
</tr>
<tr>
<td>39 years</td>
<td>4.8</td>
<td>2.9</td>
<td>8.8</td>
<td>4.4</td>
<td>9.6</td>
</tr>
</tbody>
</table>
Reclassification

The abilities of elevated 1-h and 2-h blood glucose levels to reclassify risk in addition to fasting blood glucose measurements were tested in separate models. Two risk categories were applied, and reclassification could only be present if postload glucose levels were elevated in subjects with normal fasting glucose. As such, the addition of 1-h glucose was associated with greater net reclassification improvement than the addition of 2-h glucose at both 12 years (0.308 vs. 0.066) and 39 years (0.214 vs. 0.016) (Supplementary Table 4).

Guideline-Based Screening

Restricting analyses to subjects in whom contemporary guidelines suggest screening for diabetes (8), i.e., subjects aged ≥45 years or subjects with a BMI ≥25 kg/m² and at least one additional risk factor (> 99% of our study population met the criteria for screening) did not alter the results.

Diabetes Complications and Mortality

Similar overall patterns were observed when we used all-cause mortality as the outcome, i.e., subjects with elevated 1-h blood glucose levels had a significantly higher mortality risk than those with NGT/1h-normal, whereas those with IGT/1h-normal did not (Table 3, Supplementary Table 5, and Fig. 1B). The risk of myocardial infarction or fatal ischemic heart disease was also greater among subjects with elevated 1-h glucose levels versus NGT/1h-normal. Finally, elevated 1-h glucose levels were associated with greater risks of retinopathy and peripheral vascular complications. No differences were detected between IGT/1h-normal and NGT/1h-normal (Supplementary Tables 6 and 7).

Glucose Measurements at Earlier Time Points

To highlight the importance of 1-h blood glucose measurements, we performed supplemental analyses comparing glucose levels obtained at 20 and 40 min with those obtained at fasting, 1 h, and 2 h in predicting incident type 2 diabetes and all-cause mortality (Supplementary Tables 8 and 9). Standardized HRs for glucose measurements obtained at time points earlier than 2 h were generally greater among the younger and thinner halves of the study population, but only the interaction terms between BMI and 40-min and 1-h glucose, and between age and 40-min glucose, were statistically significant (Supplementary Table 10).

Female Subjects

Median age at baseline was 39 years (IQR 38–40; range 29–56). Median follow-up was 36 years (IQR 35–36). Mean blood glucose concentrations were 4.7 ± 0.5 mmol/L (84 ± 8 mg/dL) at fasting, 7.5 ± 1.9 mmol/L (135 ± 34 mg/dL) at 1 h, and 5.8 ± 1.2 mmol/L (104 ± 22 mg/dL) at 2 h. Four (3%) had an elevated 2-h glucose concentration, and 41 (32%) had an elevated level at 1 h. Accordingly, 86 (67%) were categorized as NGT/1h-normal, 38 (30%) were categorized as NGT/1h-high, 1 (1%) was categorized as IGT/1h-normal, and 3 (2%) were categorized as IGT/1h-high. None had developed type 2 diabetes at 12 years. At complete follow-up, 13 (10%) had been diagnosed with type 2 diabetes, corresponding to an incidence density of 3.2/1,000 person-years. Cumulative incidences (and incidence densities per 1,000 person-years) in the four categories were 8% (2.5), 13% (4.2), 0% (0), and 33% (13.6), respectively. Compared with the NGT/1h-normal group, HRs were 1.72 (95 CI 0.55–5.43), P = 0.35, for the NGT/1h-high
CONCLUSIONS

Our results demonstrate that in middle-aged men, for whom screening for type 2 diabetes would be recommended, the 1-h blood glucose level is a significant predictor of future type 2 diabetes, regardless of the 2-h blood glucose level. In addition, the 1-h blood glucose level has greater detection rates (higher sensitivity) than the 2-h blood glucose level and can correctly reclassify subjects with traditionally defined prediabetes, especially with longer duration of follow-up (high specificity). Importantly, the 1-h blood glucose level is also associated with diabetes complications and mortality.

Prior studies have focused mainly on the ability of 1-h glucose measurements to correctly subdivide subjects with NGT into those with low(er) and high(er) risk of future type 2 diabetes and focused less on the direct comparison between 1-h and 2-h OGTT from a clinical standpoint (10,12,13). The proposed cut point for 1-h blood glucose levels predicted incidence (performs equivalent to or better than conventional IGT) constituted a minority (18), and, importantly, few individuals categorized as such progressed to diabetes, without any significant difference from persons in the NGT/1h-normal group. Conversely, the IGT/1h-high subgroup contained individuals at very high risk of future type 2 diabetes. Therefore, virtually all individuals with true IGT at 2 h who progressed to manifest type 2 diabetes were captured by an elevated 1-h glucose level.

The ability of 1-h blood glucose levels to predict diabetes complications and mortality is less well studied. Elevated glucose levels at 1 h are associated with adverse metabolic and cardiovascular changes, reflected by body composition, cholesterol levels, and subclinical target organ damage, including arterial stiffness, carotid intima-media thickness, and left ventricular hypertrophy (19,20,29–31). However, very few reports of the clinical consequences have been published (32–35), and although associations with microvascular events and mortality have been shown, only one study of 1,945 subjects included glucose levels at 2 h and indicated that 1-h glucose levels predicted all-cause mortality among subjects with NGT (35). Our study demonstrates for the first time an association between elevated 1-h blood glucose levels and adverse cardiovascular prognosis, including microvascular complications, in subjects with NGT, while at the same time showing the lack of such an association in subjects with IGT only. Furthermore, the 1-h blood glucose level predicted mortality, whereas isolated IGT did not.

Although the 2-h OGTT has received less emphasis by the American Diabetes Association (8), the majority of evidence for intervention among subjects with prediabetes comes from studies of overweight or obese individuals with IGT (3–6). Furthermore, both fasting glucose and HbA1c have limited sensitivity and specificity for detecting subjects at risk, especially because of high false-negative rates, and the current study provides evidence that the 1-h OGTT is superior to fasting glucose alone for identifying high-risk subjects (7,10,12,13,15,16,36–38). Hence, a more sensitive strategy is needed, which at the same time is simple to use in a primary care setting and less time consuming and more convenient than the 2-h OGTT. The current study extends the results from a previous report from the Malmö Preventive Project and shows that the 1-h time limit provides not only the best compromise in terms of time consumption (performs equivalent to or better than glucose measurement at 90 min) but also prognostic ability (performing better than glucose measurements at 20 and 40 min) (17). The proposed cut point for 1-h blood glucose identifies a substantially larger proportion of subjects at high risk compared with conventional IGT (10,12,13), and its use could lead to more widespread preventive efforts. However, since subjects for whom screening for type 2 diabetes is recommended already have an adverse risk profile (7,8), using a 1-h OGTT should lead to a reduced burden of both diabetes and its complications, without an excess risk of harm.

The pathophysiological significance of elevated 1-h blood glucose levels is not

<table>
<thead>
<tr>
<th>Table 3—Crude and adjusted HRs for incident type 2 diabetes and all-cause mortality, stratified according to glycemic category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk group*</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td><strong>Type 2 diabetes</strong></td>
</tr>
<tr>
<td>12 years</td>
</tr>
<tr>
<td>NGT/1h-high</td>
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<tr>
<td>IGT/1h-normalF</td>
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<tr>
<td>IGT/1h-high</td>
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<tr>
<td>39 years</td>
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<tr>
<td>NGT/1h-high</td>
</tr>
<tr>
<td>IGT/1h-normal</td>
</tr>
<tr>
<td>IGT/1h-high</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
</tr>
<tr>
<td>12 years</td>
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<tr>
<td>NGT/1h-high</td>
</tr>
<tr>
<td>IGT/1h-normal</td>
</tr>
<tr>
<td>IGT/1h-high</td>
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<tr>
<td>39 years</td>
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<td>NGT/1h-high</td>
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<td>IGT/1h-normal</td>
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*The NGT/1h-normal group serves as baseline (comparator group). †The multivariable Cox proportional hazards regression model was adjusted for age, BMI, IFG, triglycerides, and family history of diabetes. ‡There were no events in this small group at 12 years.

group and 6.68 (95% CI 0.82–54.52), \(P = 0.08\), for the IGT/1h-high group.
fully understood. Proposely, these individuals may be at an intermediate stage between NGT and IGT or represent a phenotype distinct from that of individuals with IGT (10, 19, 20). In subjects with NGT, an elevated 1-h glucose level is associated with insulin resistance to a degree similar to that seen among individuals with IGT. Insulin secretion is also affected, albeit to a lesser extent (19, 20). Furthermore, the risk of future type 2 diabetes associated with elevated 1-h blood glucose levels was temporally persistent but greater in the IGT/1h-high group than in the NGT/1h-normal group, particularly at shorter follow-up. These findings, in addition to those stated above, largely support the first theory and further support the concept that worsening β-cell function, not insulin resistance, is the main culprit involved in progressive glucometabolic deterioration (13).

Our results highlight the potential benefit of targeting individuals with an elevated 1-h blood glucose level and provide a strong rationale for an interventional study in which subjects are selected based on this abnormality. Should preventive efforts prove beneficial in this relatively large group, it would become prudent to consider 1-h blood glucose as a replacement for 2-h blood glucose.

A few limitations deserve mention. The definition of type 2 diabetes has changed over the past decades, notably with the lowering of the fasting glucose threshold in 1997 and the introduction of HbA_{1c} defined diabetes in 2011 (7). However, despite there being only a partial overlap between subjects with prediabetes and diabetes defined according to these different measures, the predictive capability of clinical risk factors remains comparable (7, 39). The 30 g/m² glucose load was the standard procedure at the initiation of the study, and based on estimates of body surface area, this resulted in an average glucose load 23% lower than with the use of 75-g glucose. Prior studies have suggested that a larger glucose load results in greater differences in glucose concentrations at 2 h than at 1 h. In individuals without IGT or diabetes, the glucose levels at 1 h are virtually identical when comparing a 50-g with a 100-g glucose load. Even at 2 h, the difference appears to be small, with highly correlated values (40–43). Discrepancies between glucose levels are larger among subjects with IGT at both 1 h and 2 h (42). Theoretically, the lower glucose dose might have had a slightly greater impact on the 2-h level than the 1-h level, improving the relative sensitivity of the 1-h measurement, but significant differences have not been shown for 75 g versus 100 g, and it is not likely that important differences would exist for the glucose load used in our study compared with the standard 75-g load (43). In contrast with the well-established partitions for fasting glucose and 2-h OGTT, the cut point of 8.6 mmol/L for 1-h OGTT has been less thoroughly investigated and was derived from the San Antonio Heart Study (10). However, use of a cut point derived from our cohort would have inflated its utility compared with 2-h OGTT. An additional limitation might be attributed to the use of two different approaches for measurement of glucose levels, although the glucose oxidase and hexokinase methods have been shown to deliver well-correlated results (44). The generalizability of our results beyond white men may be limited, but there is no evidence to suggest sex- or race-related differences in the prognostic ability of 1-h versus 2-h OGTT. However, women may have slightly lower mean concentrations of 1-h glucose, with a slower return to baseline levels (45). This fits well with the observation that traditionally defined IGT is more prevalent in females than in males (9). Most women were recruited later during the Malmö Preventive Project, when routine performance of the comprehensive OGTT had been omitted owing to financial restrictions. Thus, very few women underwent such testing and the results obtained from this subgroup should be interpreted very cautiously, given the minuscule number of events. The isolated IGT group was small, and although results were consistent, CIs were wide. Still, this finding by itself is valuable, as it indicates a minimal loss by not capturing these individuals. Finally, although we excluded the individuals who underwent lifestyle intervention to enhance the interpretability of our study, this might have resulted in removal of the subjects who had the highest a priori risk for type 2 diabetes and associated complications, underestimating the true incidence of outcomes, particularly in the subgroups with abnormal baseline glycemic status.

In conclusion, the 1-h blood glucose level is a powerful predictor of future type 2 diabetes, with net reclassification improvement and detection rates significantly greater than 2-h blood glucose measurements, especially with longer duration of follow-up. The 1-h blood glucose level is further associated with diabetes complications and mortality. Finally, simple logistics favor the use of a 1-h versus a 2-h OGTT. Therefore, 1-h blood glucose should be considered as a replacement for 2-h blood glucose as the preferred marker of IGT.

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revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved. M.P. and M.H.O. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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