Incidence of type 2 diabetes using proposed HbA$_{1c}$ diagnostic criteria in the EPIC-Norfolk cohort: implications for preventive strategies

Short running title: Incidence of type 2 diabetes using proposed HbA$_{1c}$ diagnostic criteria

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

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Objectives: To evaluate the incidence and relative risk of type 2 diabetes defined by the newly proposed HbA$_{1c}$ diagnostic criteria in groups categorised by different baseline HbA$_{1c}$ levels.

Research Design and Methods: Using data from the EPIC-Norfolk cohort with repeat HbA$_{1c}$ measurements, we estimated the prevalence of known and previously-undiagnosed diabetes at baseline (baseline HbA$_{1c}$ ≥6.5%) and the incidence of diabetes over 3 years. We also examined the incidence and corresponding odds ratios (OR) by different levels of baseline HbA$_{1c}$. Incident diabetes was defined clinically (self-report at follow-up, prescribed diabetes medication or inclusion on a diabetes register) and/or biochemically (HbA$_{1c}$ ≥6.5% at the second health assessment).

Results: Overall prevalence of diabetes was 4.7%; 41% of prevalent cases were previously undiagnosed. Among 5,735 participants without diabetes at baseline (identified clinically and/or using HbA$_{1c}$ criteria), 72 developed diabetes over 3 years (1.3%; 95%CI 1.0-1.5), of which half (49%) were identified using the HbA$_{1c}$ criteria. Six percent of the total population had a baseline HbA$_{1c}$ in the range 6.0-6.4%; one-third of incident cases arose in this group. Incidence of diabetes in this group was 15 times higher than in those with a baseline HbA$_{1c}$ of <5.0% (OR 15.5; 95%CI 7.2-33.3).

Conclusions: The cumulative incidence of diabetes defined using a newly proposed HbA$_{1c}$ threshold in this middle-aged British cohort was 1.3% over 3 years. Targeting interventions to individuals with an HbA$_{1c}$ of 6.0-6.4% might represent a feasible preventive strategy, although complementary population-based preventive strategies are also needed to reduce the growing burden of diabetes.

Type 2 diabetes is a major public health concern worldwide. It is estimated that 439 million people will have the disease by 2030.(1) It is possible to halve the incidence of type 2 diabetes among individuals at high risk through lifestyle and pharmacological interventions.(2-4) However, it is unlikely that population screening for impaired glucose tolerance using an oral glucose tolerance test (OGTT) is a feasible method of identifying those at high risk in clinical practice,(5) as it is time- and resource-consuming, and has poor reproducibility.(6) If a measure of blood glucose is to be used to define risk of developing diabetes, then it would seem logical to use the same test for diagnosis and informing treatment decisions.(7) Glycated haemoglobin (HbA$_{1c}$) is a reliable measure of long-term glycaemic exposure(8) which correlates well with the risk of micro- and macrovascular complications of diabetes.(9; 10) It does not necessitate fasting or timed blood samples. Previous concerns regarding the standardisation of assays have largely been resolved.(11) Consequently, the American Diabetes Association (ADA) recently recommended that HbA$_{1c}$ be included as a diagnostic test for diabetes, with a diagnostic threshold of ≥6.5%.(12) In order to better estimate the burden of the disease and potential benefits of preventive interventions, it is necessary to have accurate data on incidence. Reported estimates of incidence in adult populations
have varied considerably from 2 to 25 per
1,000 person-years. (13-16) However, many
of the studies were restricted to high risk
populations (13) and defined diabetes using
a clinical rather than a biochemical
diagnosis. (14) Fewer studies have
investigated the incidence of diabetes based
on longitudinal repeat blood glucose
measurements in population-based
samples, (15; 16) and none have examined
diabetes incidence using repeated
measures of HbA\textsubscript{1c}.
In this study we estimated the prevalence
and incidence of diabetes defined using the
newly proposed HbA\textsubscript{1c} cut-off point of 6.5%
in a population-based British cohort. To
inform the choice of appropriate HbA\textsubscript{1c}
thresholds to identify individuals at high risk
to whom preventive interventions might be
offered, we used data on longitudinal repeat
HbA\textsubscript{1c} values at baseline and after 3 years
of follow-up to examine the incidence and
relative risk of clinically diagnosed diabetes
and diabetes defined using HbA\textsubscript{1c} diagnostic
criteria in groups defined by different
baseline HbA\textsubscript{1c} values.

RESEARCH DESIGN AND METHODS:
Study design and population. The
European Prospective Investigation of
Cancer-Norfolk (EPIC-Norfolk) is a
population-based prospective study that
follows 25,639 men and women aged 40-74
years residing in the Norfolk region, United
Kingdom. Details of the study have been
described elsewhere. (17) In brief, between
1993 and 1997, 77,630 individuals were
recruited from general practice to participate
in the study. Of these, 25,639 (33%) consented and attended a baseline health
assessment. Participants completed
questionnaires about their personal and
family history of disease, medication, and
lifestyle factors including smoking habits.
They were asked whether a physician had
ever told them that they had any of the
conditions in a list that included diabetes,
heart attack, and stroke. Additionally,
baseline diabetes status was ascertained by
1) self report of diabetes medication, 2)
diabetes medication brought to the baseline
examination, 3) participants indicating
modification of their diet in the past year
because of diabetes mellitus, or 4) participants indicating adherence to a
diabetic diet. Anthropometric and blood
pressure measurements, and non-fasting
blood samples were also taken at the health
assessment. As funding for measurement of
glycated hemoglobin (HbA\textsubscript{1c}) only became
available in 1995, around half of all
participants had information on this measure
at baseline. HbA\textsubscript{1c} was measured on fresh
EDTA blood samples using high-
performance liquid chromatography (Diamat
Automated Glycated Hemoglobin Analyzer;
Bio-Rad Laboratories Ltd, Hemel Hemstead,
England), which was standardized to the
DCCT assay. Participants were invited to
attend a second health assessment after 3
years (1998-2001), at which identical
measurements were taken. 15,028
participants (59%) attended the second
health assessment. General practitioners of
participants whose test results were
abnormal (HbA\textsubscript{1c} ≥ 7.0) were notified so that
they could assume responsibility for
confirming diagnosis and arranging
treatment. The study was approved by the
Norwich District Health Authority Ethics
Committee. All participants gave signed
informed consent.
The Norfolk area is slightly healthier than
the general UK population, with a
standardized mortality ratio of 93 (source:
Office for National Statistics death
registration data, 2008). However, EPIC-
Norfolk is similar to a nationally
representative sample regarding
anthropometric indices, blood pressure and
serum lipids. (17)
We report results for follow-up to the second health assessment, a median of 3 years. We limited our analyses to individuals with HbA1c measurements at baseline and at the second health assessment (n=6,372). We used this study sample to estimate prevalence of known (clinically diagnosed diabetes: self-reported physician diagnosed diabetes and diabetes medication) and previously undiagnosed diabetes at baseline (baseline HbA1c ≥6.5%). After excluding those with diabetes at baseline (clinically diagnosed diabetes and diabetes defined using HbA1c diagnostic criteria), we further excluded those with missing data for other metabolic risk factors, e.g. age, sex, a family history of diabetes, smoking, the use of corticosteroids and anti-hypertensive drugs, body mass index (BMI), waist circumference, systolic blood pressure, cholesterol, and triglyceride (n=335), leaving 5,735 individuals for analyses of the incidence and risk of diabetes (Figure 1).

Ascertainment of incident diabetes. Participants were identified as having incident diabetes if 1) they reported physician-diagnosed diabetes or diabetes medication, or brought diabetes medication to the second health assessment (clinical diagnosis), 2) they were identified on medical records, diabetes registers or death certificates (clinical diagnosis) and/or 3) they had an HbA1c of ≥6.5% at the second health assessment (HbA1c-defined diabetes). Participants were identified via their general practice diabetes register or the Norfolk and Norwich Hospital diabetes register. Participants admitted to a hospital with a diabetes-related condition were identified by their National Health Service number. Hospitals were linked to the East Norfolk Health Authority database, which identifies all hospital contacts throughout England and Wales for Norfolk residents. Vital status for all EPIC-Norfolk participants was obtained via death certification at the Office for National Statistics, and death certification with coding for diabetes was identified. Previous validation studies in this cohort using capture-recapture analysis indicated that using multiple sources of ascertainment information for diabetes detected 99% of incident cases, when comparing with diagnostic information from a comprehensive review of medical records.(18)

Statistical analyses. In 5,735 participants free of diabetes at baseline with data on HbA1c for the baseline and second health assessments, we calculated the incidence of diabetes defined clinically and using HbA1c diagnostic criteria in the whole cohort and separately for different categories of baseline HbA1c. Baseline characteristics were summarised for groups defined by different categories of baseline HbA1c (<5.0%, 5.0-5.4%, 5.5-5.9%, and 6.0-6.4%). We tested for differences between groups using the χ² test for categorical variables, and analysis of variance or Kruskal-Wallis tests for normally or non-normally distributed continuous variables respectively.

We used logistic regression to estimate the risk of developing diabetes as measured by the odds ratios (OR) for every 0.5% increase in HbA1c, as well as for different categories of HbA1c compared to the lowest HbA1c category of <5.0%. We examined odds ratios adjusted for age only, age and sex only, and multiple risk factors (age, sex, self-reported family history of diabetes, smoking, the use of anti-hypertensive drugs or corticosteroids, BMI, waist circumference, systolic blood pressure, total cholesterol, HDL cholesterol and triglyceride). To inform alternative screening strategies, we investigated risk factors associated with incident diabetes in those with a baseline HbA1c of <6.0%.

We also performed a sensitivity analysis using a more restricted definition of incident diabetes, in which participants were not
classified as having incident diabetes unless a self-reported diagnosis was supported by information on diabetes specific medication or confirmed by information from clinical records, death certificates or HbA1c.

RESULTS
Table 1 summarises baseline characteristics of participants in the EPIC-Norfolk cohort by different HbA1c categories. The mean age of participants was 57.4 (SD=9.4) years, and 45% were male. Participants with a higher HbA1c value were older, more likely to be male, obese, current smokers, and to come from a lower socioeconomic class than those with a lower HbA1c value. They were also more likely to have higher blood pressure, total cholesterol and triglyceride values, and lower HDL cholesterol values. There was no difference in family history of diabetes and the use of corticosteroids between groups.

Prevalence of diabetes at baseline. Among 6,372 individuals with HbA1c measurements at both health assessments, 302 individuals (4.7%) had prevalent diabetes at baseline (Figure 1). Among these cases, 178 (2.8%) had known diabetes (those identified clinically), while 124 (1.9%) had previously undiagnosed diabetes (those identified using HbA1c criteria).

Incidence of diabetes over 3 years. Among 5,735 participants free of diabetes at baseline, 72 developed diabetes over 3 years (Figure 1). The cumulative incidence was 1.3% (95%CI 1.0-1.5) over 3 years, an annual incidence of 0.4%. Among these new cases of diabetes, 37 (51%) were identified clinically e.g. by their response to the questionnaire at the second health check or through linkage to clinical records or diabetes registers (incidence 0.6%; 95%CI 0.4-0.9). The remaining half of incident cases (35 individuals (49%)) were identified on the basis of their HbA1c results at the second health assessment.

Risk of developing diabetes in groups defined by different HbA1c levels. Table 2 shows the incidence of diabetes by baseline HbA1c levels for clinical diagnosis only, and for clinical and/or HbA1c-defined diagnosis. The incidence of diabetes increased progressively with increasing baseline HbA1c levels. In those with a baseline HbA1c of 6.0–6.4%, the incidence of clinically diagnosed and/or HbA1c-defined diabetes was 3 times higher than that of clinically diagnosed diabetes (7.0; 95%CI 4.8-10.1 and 2.4; 95%CI 1.3-4.6 respectively). One-third of incident cases of diabetes arose from individuals with a baseline HbA1c of 6.0-6.4% (6% of the total population), and just over one-third of incident cases arose among individuals with a baseline HbA1c of <5.5% (69% of the total population). There were significant positive associations between HbA1c and the risk of developing diabetes (Table 2). A 0.5% increase in baseline HbA1c was associated with more than a 2-fold increase in risk of clinically diagnosed and/or HbA1c-defined diabetes (age-adjusted OR 2.7; 95%CI 2.1-3.5). Participants with a baseline HbA1c of 6.0-6.4% had around a 7-fold higher risk of clinically diagnosed diabetes than those with an HbA1c of <5.0%. The highest risk of clinically diagnosed and/or HbA1c-defined diabetes was observed in the highest baseline HbA1c category compared to those with a baseline HbA1c of <5.0% (OR 15.5; 95%CI 7.2-33.3). These ORs remained unchanged after adjustment for other risk factors.

Among individuals with a baseline HbA1c <6.0%, a family history of diabetes and waist circumference were the strongest non-laboratory predictors of incident diabetes over 3 years.

In the sensitivity analysis using a more restricted definition of incident diabetes, 59
individuals developed diabetes (Online Appendix Table 1, available at http://care.diabetesjournals.org). The incidence was 1.0 (95%CI 0.8-1.3) over 3 years, an annual incidence of 0.3%. The majority of incident cases (37 individuals (63%)) were identified using HbA1c diagnostic criteria. Around 40% of incident cases of diabetes developed in individuals with a high baseline HbA1c of 6.0-6.4% (6% of total population). A 27-fold higher risk of diabetes was observed in those with a baseline HbA1c of 6.0-6.4%, compared to those with a baseline HbA1c of <5.0%.

CONCLUSIONS
Using data from a large population-based British prospective cohort, we estimated the prevalence and incidence of diabetes defined clinically and/or by HbA1c over 3 years. Half of new cases were identified by the HbA1c diagnostic threshold of 6.5%. The incidence of diabetes increased progressively across baseline HbA1c levels. One-third of incident cases developed in individuals with a baseline HbA1c of 6.0-6.4%. To the best of our knowledge, this study is the first to report the incidence of diabetes based on HbA1c diagnostic criteria using repeated assessment of HbA1c. Our prevalence estimate is comparable with the prevalence of diabetes in England (4.4%) estimated from an epidemiological model in which known and previously undiagnosed diabetes were included.(19) We also found that around 40% of prevalent cases were identified using HbA1c diagnostic criteria, and hence were previously undiagnosed. This is consistent with previous studies using an OGTT as a screening test.(20)

A number of studies have estimated diabetes incidence based on longitudinal repeat OGTT or fasting plasma glucose (FPG) measurements.(15; 16) In these studies, the incidence of diabetes varied from 6% to 10% over 9-10 years. Data from a British population in Ely, Cambridgeshire, showed that the cumulative incidence of diabetes using repeat OGTT measurements was 5.9% over 10 years, corresponding to an annual incidence of 0.6%.(16) This is comparable with the low annual incidence of 0.4% in the present study. The higher incidence in the earlier study may be explained by enhanced case detection from repeated testing by OGTT over a longer period (OGTT testing at baseline, 4.5 and 10 years in the earlier Ely study vs. HbA1c at baseline and after 3 years of follow-up in the EPIC-Norfolk study) and the different contributions of the “healthy volunteer effect” in each study (response rates: 74% and 33% in the Ely and EPIC-Norfolk study respectively).

Few studies have examined the incidence and relative risk of diabetes in individuals or groups defined by different baseline HbA1c levels. Selvin et al. examined the incidence of self-reported diabetes in American men and women with different baseline HbA1c values.(21) The 15-year cumulative incidence of diabetes was 6%, 12%, 21% and 44% in individuals with an HbA1c of <5.0, 5.0-5.4%, 5.5-5.9% and 6.0-6.4% respectively. The estimated annual incidence was higher than those observed across all HbA1c categories in our study. It might be explained by the differences in levels of other risk factors (higher BMI, smoking and family history of diabetes in Selvin’s study), follow-up time (15 vs. 3 years, if incidence rates are not consistent across different durations of follow-up) and in particular the different definitions of diabetes used in each study.

HbA1c has been shown to be a useful tool for the early detection of diabetes.(21) A few studies have demonstrated that HbA1c predicts future risk of diabetes in high risk individuals with glucose intolerance.(22) We have shown that HbA1c predicts risk of
diabetes in healthy middle-age men and women. An HbA\textsubscript{1c} of 6.0-6.4% identified one-quarter of clinically incident diabetes, and one-third of clinically incident and/or HbA\textsubscript{1c}-defined diabetes. These figures were even higher when a more restricted definition of incident diabetes was used. Recent evidence shows that this predictive ability also holds true in low risk non-diabetic men and women(21) and in the elderly.(23) However, given that the associations between HbA\textsubscript{1c} and risk of diabetes were hardly changed following adjustment for multiple risk factors, there may not be much to gain from including data on multiple risk factors alongside HbA\textsubscript{1c} for diabetes risk prediction.

The ADA suggested that there was no specific threshold which defines individuals who might be offered preventive interventions and that any such threshold would vary between countries with different health care priorities.(12) However, they suggested that individuals with an HbA\textsubscript{1c} between 6.0% and 6.4% might represent a group in whom the risk of development of diabetes was very high and who could therefore be targeted for individual prevention interventions.(12) They also suggested that this range should not be considered an absolute threshold and that interventions may be appropriate in other individuals based on other risk information. Our findings support this statement by demonstrating that the majority of new cases of diabetes developed in those with a baseline HbA\textsubscript{1c} <6.0%.

The selection of a population for a high risk prevention strategy is based on the level of risk identified, the proportion of the population to be targeted and the proportion of future cases that might therefore be prevented. Our study has shown that one-third of new cases of diabetes arose from the 6% of the study population who had the highest glycaemic levels (HbA\textsubscript{1c} 6.0-6.4%). Indeed, if previously proven intensive prevention interventions(2; 3) were targeted at this middle-aged population, around 20% of new cases of diabetes could be prevented over 3 years. Strategies for identifying which individuals should have an HbA\textsubscript{1c} measurement including either simple risk scores using easily-measured or routinely available risk factors are needed. Although the category of people with an HbA\textsubscript{1c} of 6.0-6.4% identifies a high risk group, the majority of new cases of diabetes developed in individuals whose baseline HbA\textsubscript{1c} values were under 6%. Complementary strategies to identify high risk individuals among those without raised HbA\textsubscript{1c} may therefore be necessary. Our subgroup analysis in individuals with an HbA\textsubscript{1c} <6.0% suggested that those with central obesity and a family history of diabetes might represent another relatively-easily identifiable subgroup to whom preventive interventions could be targeted. This also suggests that in addition to high-risk approaches, we need to develop a complementary population-based strategy aimed at shifting the whole distribution of HbA\textsubscript{1c} in the population to reduce the risk of both diabetes and its complications.(24) However, while there is some evidence for the cost-effectiveness of prevention interventions among high risk individuals,(25) evidence on the cost-effectiveness of population-based strategies is very limited, making judgements about the balance of investment in high risk and population-based approaches difficult.

We have reported the incidence of diabetes in a large prospective British cohort using both clinical ascertainment and newly proposed HbA\textsubscript{1c} diagnostic criteria. Participants included in this analysis were healthier than those excluded, hence our findings are likely to underestimate the incidence of diabetes in the whole cohort. Given the 33% recruitment rate in this study,
it is possible that participants might be more health-conscious, and more likely to engage in healthy behaviours and to take up existing preventive services, compared to non-participants. We might therefore have underestimated the overall incidence of diabetes in the population, which might consequently influence estimates of the relative risk for HbA1c.

As the EPIC-Norfolk study collected non-fasting blood samples, it is not possible to compare the predictive ability for incident diabetes of different measures of glycaemia. Similar to other diagnostic tests, using a single measure of HbA1c for diagnosing diabetes might lead to some degree of misclassification. However, given that HbA1c is more reliable compared to an OGTT and FPG, the misclassification is likely to be only modest. A relative short follow-up period and relatively small number of events mean that our finding should be interpreted with caution. However, our study is one of the largest incidence studies reported. Furthermore, the follow-up of 3 years is still a plausible and important timeframe for identifying those at high risk of diabetes as in addition to long-term risk information, one might also be interested in and more persuaded for behaviour modification by information on short-term risk of diabetes. Our findings were specific to a middle-aged population (aged 40-74 years) and may not represent the burden and risk of diabetes in relation to HbA1c levels in younger people. Lastly, as the majority of EPIC-Norfolk participants are of European descent, the generalisability of our findings to other ethnic groups and populations is limited.

In conclusion, the cumulative incidence of diabetes defined using a newly proposed HbA1c threshold in this middle-aged British cohort was 1.3% over 3 years (0.4% per year). HbA1c independently predicted the risk of incident diabetes with each 0.5% difference in HbA1c being associated with a more than doubling of the risk of diabetes. As one-third of incident cases of diabetes came from the 6% of the population with baseline HbA1c between 6 and 6.5%, this may be an easily identifiable sub-group to whom preventive interventions could be targeted. However, alternative strategies to identify high risk individuals may be necessary and complementary population-based approaches need to be developed to shift the underlying distribution of glycaemia.

**Author Contributions:** PC researched data, contributed to discussion, wrote manuscript, reviewed/edited manuscript. RKS researched data, contributed to discussion, reviewed/edited manuscript. RNL researched data, contributed to discussion, reviewed/edited manuscript. NGF researched data, contributed to discussion, reviewed/edited manuscript. K-TK researched data, reviewed/edited manuscript. NJW researched data, contributed to discussion, reviewed/edited manuscript. SJG researched data, contributed to discussion, reviewed/edited manuscript.

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preparation, review, approval, or decision to submit this manuscript for publication.

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REFERENCES


Table 1. Comparison of baseline characteristics across categories of baseline HbA\(_1c\) in 5,735 participants in the EPIC-Norfolk cohort.

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<th>Total</th>
<th>Hba(_1c) level</th>
<th>p-value for difference *</th>
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<tr>
<td></td>
<td>&lt; 5.0%</td>
<td>5.0 – 5.4%</td>
<td>5.5 – 5.9%</td>
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<tr>
<td>Number (%)</td>
<td>5,735 (100)</td>
<td>1,849 (32.2)</td>
<td>2,119 (36.9)</td>
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<tr>
<td>Age, years</td>
<td>57.4 (9.4)</td>
<td>54.1 (9.2)</td>
<td>57.4 (9.1)</td>
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<td>Men, No (%)</td>
<td>2,481 (43.3)</td>
<td>746 (40.4)</td>
<td>932 (44.0)</td>
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<td>Social class(^\d), No (%)</td>
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<tr>
<td>class I-IIIa</td>
<td>3,694 (64.4)</td>
<td>1,255 (67.9)</td>
<td>1,358 (64.1)</td>
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<td>class IIIb-V</td>
<td>2,041 (35.6)</td>
<td>594 (32.1)</td>
<td>761 (35.9)</td>
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<td>Current smokers, No (%)</td>
<td>525 (9.2)</td>
<td>141 (7.6)</td>
<td>165 (7.8)</td>
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<td>Family history of diabetes, No (%)</td>
<td>697 (12.2)</td>
<td>217 (11.7)</td>
<td>250 (11.8)</td>
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<td>Use of corticosteroids, No (%)</td>
<td>156 (2.7)</td>
<td>44 (2.4)</td>
<td>61 (2.9)</td>
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<td>Use of anti-hypertensive drugs, No (%)</td>
<td>811 (14.1)</td>
<td>188 (10.2)</td>
<td>301 (14.2)</td>
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<td>BMI category, No (%)</td>
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<tr>
<td>&lt; 25 kg/m(^2)</td>
<td>2,528 (44.1)</td>
<td>935 (50.6)</td>
<td>906 (42.8)</td>
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<td>25-29.9 kg/m(^2)</td>
<td>25,24 (44.0)</td>
<td>738 (39.9)</td>
<td>956 (45.1)</td>
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<td>&gt;=30 kg/m(^2)</td>
<td>683 (11.9)</td>
<td>176 (9.5)</td>
<td>257 (12.1)</td>
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<td>Waist circumference, cm</td>
<td>86.9 (12.2)</td>
<td>84.8 (12.2)</td>
<td>87.1 (11.9)</td>
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<td>Systolic blood pressure, mm Hg</td>
<td>133.4 (17.5)</td>
<td>130.6 (17.1)</td>
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<td>Diastolic blood pressure, mm Hg</td>
<td>82.0 (10.8)</td>
<td>80.9 (10.6)</td>
<td>82.1 (10.8)</td>
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<td>Total cholesterol, mmol/l</td>
<td>6.1 (1.1)</td>
<td>5.8 (1.1)</td>
<td>6.1 (1.1)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.4)</td>
</tr>
<tr>
<td>Triglyceride, mmol/l, median (interquartile range)</td>
<td>1.4 (1.0 – 2.1)</td>
<td>1.3 (0.9 – 1.8)</td>
<td>1.5 (1.0 – 2.1)</td>
</tr>
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Data are presented in mean (standard deviation), unless specified otherwise. * differences between groups using \(\chi^2\) tests for categorical variables, and analysis of variance (ANOVA) or Kruskal-Wallis tests for normally or non-normally distributed continuous variables.

\(^\d\) Registrar General's Social Class: class I = Professional, etc. occupations, II = Managerial and Technical occupations, IIIa = Skilled occupations (non-manual), IIIb = Skilled occupations (manual), IV = Partly-skilled occupations, V = Unskilled occupations.
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<tr>
<td>Clinically diagnosed diabetes</td>
<td>Total</td>
<td>5,735</td>
<td>1,849 (32%)</td>
<td>2,119 (37%)</td>
<td>1,397 (24%)</td>
<td>370 (6%)</td>
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<tr>
<td></td>
<td>Number</td>
<td>37</td>
<td>7 (19%)</td>
<td>6 (16%)</td>
<td>15 (41%)</td>
<td>9 (24%)</td>
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<td></td>
<td>3-yr cumulative incidence (%)</td>
<td>0.6 (0.4 – 0.9)</td>
<td>0.4 (0.2 – 0.8)</td>
<td>0.3 (0.1 – 0.6)</td>
<td>1.1 (0.6 – 1.8)</td>
<td>2.4 (1.3 – 4.6)</td>
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<tr>
<td></td>
<td>Unadjusted OR</td>
<td>1.0</td>
<td>0.7 (0.3 – 2.2)</td>
<td>2.9 (1.2 – 7.0)</td>
<td>6.6 (2.4 – 17.7)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Age-adjusted OR</td>
<td>1.0</td>
<td>0.8 (0.3 – 2.4)</td>
<td>3.3 (1.3 – 8.4)</td>
<td>8.0 (2.8 – 22.7)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Age- and sex-adjusted OR</td>
<td>1.0</td>
<td>0.8 (0.3 – 2.4)</td>
<td>3.3 (1.3 – 8.3)</td>
<td>7.9 (2.8 – 22.4)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>Multivariable-adjusted OR*</td>
<td>1.0</td>
<td>0.8 (0.3 – 2.3)</td>
<td>3.0 (1.2 – 7.8)</td>
<td>6.8 (2.3 – 20.1)</td>
<td>&lt;0.001</td>
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<tr>
<td>Clinically diagnosed and/or Hba1c-defined diabetes</td>
<td>Total</td>
<td>5,735</td>
<td>1,849 (32%)</td>
<td>2,119 (37%)</td>
<td>1,397 (24%)</td>
<td>370 (6%)</td>
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<tr>
<td></td>
<td>Number</td>
<td>72</td>
<td>9 (13%)</td>
<td>16 (22%)</td>
<td>21 (29%)</td>
<td>26 (36%)</td>
<td></td>
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<tr>
<td></td>
<td>3-yr cumulative incidence (%)</td>
<td>1.3 (1.0 – 1.5)</td>
<td>0.5 (0.3 – 0.9)</td>
<td>0.8 (0.5 – 1.2)</td>
<td>1.5 (1.0 – 2.3)</td>
<td>7.0 (4.8 – 10.1)</td>
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<tr>
<td></td>
<td>Unadjusted OR</td>
<td>1.0</td>
<td>1.6 (0.7 – 3.5)</td>
<td>3.1 (1.4 – 6.8)</td>
<td>15.5 (7.2 – 33.3)</td>
<td>&lt; 0.001</td>
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<tr>
<td></td>
<td>Age-adjusted OR</td>
<td>1.0</td>
<td>1.6 (0.7 – 3.8)</td>
<td>3.5 (1.6 – 7.8)</td>
<td>18.0 (8.1 – 40.0)</td>
<td>&lt; 0.001</td>
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<tr>
<td></td>
<td>Age- and sex-adjusted OR</td>
<td>1.0</td>
<td>1.6 (0.7 – 3.7)</td>
<td>3.4 (1.5 – 7.7)</td>
<td>17.7 (8.0 – 39.5)</td>
<td>&lt; 0.001</td>
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<tr>
<td></td>
<td>Multivariable-adjusted OR*</td>
<td>1.0</td>
<td>1.6 (0.7 – 3.6)</td>
<td>3.3 (1.5 – 7.4)</td>
<td>15.6 (6.9 – 35.7)</td>
<td>&lt; 0.001</td>
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</tbody>
</table>

* adjusted for age, sex, social class, self-reported family history of diabetes, smoking, use of corticosteroids and anti-hypertensive drugs, body mass index, waist circumference, systolic blood pressure, cholesterol, HDL-cholesterol and triglyceride
Figure legends
Figure 1. Schematic diagram demonstrating the number and percentage of individuals with prevalent and incidence diabetes in a cohort of 6,372 men and women over 3 years, individuals with clinically diagnosed diabetes and HbA$_1c$ $\geq$ 6.5% were considered to have clinically diagnosed diabetes in this diagram

* This included self-reported diabetes, evidence of diabetes medications and dietary modification due to diabetes.
† This included self-reported diabetes, evidence of diabetes medication, diabetes registers, hospitalisations with diabetes, and diabetes codes on death certificates.