Risk of cardiovascular disease and death in individuals with pre-diabetes defined by different criteria: The Whitehall II study

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Abstract

Objective: We compared the risk of cardiovascular disease (CVD) and all-cause mortality in subgroups of pre-diabetes defined by fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG) or HbA_{1c}.

Research Design and Methods: In the Whitehall II cohort, 5,427 participants aged 50-79 years, and without diabetes were followed for a median of 11.5 years. A total of 628 (11.6%) had pre-diabetes by the World Health Organization (WHO)/International Expert Committee (IEC)- criteria (FPG 6.1-6.9 mmol/L and/or HbA_{1c} 6.0-6.4%), and 1,996 (36.8%) by the American Diabetes Association (ADA)- criteria (FPG 5.6-6.9 mmol/L and/or HbA_{1c} 5.7-6.4%). In a subset of 4,730 individuals with additional measures of 2hPG, 663 (14.0%) had pre-diabetes by 2hPG. Incidence rates of a major event (non-fatal/fatal CVD or all-cause mortality) were compared for different definitions of pre-diabetes, adjusting for relevant confounders.

Results: Compared with normoglycaemia, incidence rates in pre-diabetes was 54% higher with the WHO/IEC-definition and 37% higher with the ADA-definition ($P<0.001$), but declining to 17% and 12% after confounder adjustment ($P\geq0.111$). Pre-diabetes by HbA_{1c} was associated with a doubling in incidence rate for both the IEC and ADA criteria. However, upon adjustment, excess risk was reduced to 13% and 17% ($P\geq0.055$), respectively. Pre-diabetes by FPG or 2hPG was not associated with an excess risk in the adjusted analysis.

Conclusions: Pre-diabetes defined by HbA_{1c} was associated with a worse prognosis than pre-diabetes defined by FPG or 2hPG. However, the excess risk among individuals with pre-

diabetes is mainly explained by the clustering of other cardiometabolic risk factors associated with hyperglycaemia.

In 1979-1980, the world health organization (WHO), the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and other diabetes organisations made a common agreement regarding the diagnostic criteria for diabetes and impaired glucose tolerance (IGT) based on the oral glucose tolerance test (OGTT) (1, 2). Since then, the diagnostic criteria for diabetes and pre-diabetes have changed several times, and there is currently no consensus on the definition of pre-diabetes between the different organisations worldwide (3-5). It is generally accepted that diabetes and pre-diabetes can be diagnosed on the basis of measures of fasting plasma glucose (FPG), 2-hour plasma glucose (2hPG) after an OGTT, or by using haemoglobin A_{1c} (HbA_{1c}). In clinical practice, FPG and HbA_{1c} are preferred over the OGTT which is inconvenient, less reproducible, and more costly. However, the cut-points for FPG and HbA_{1c} vary by the different organisations. In 2003, ADA suggested to lower the cut-point for impaired fasting glycaemia (IFG) from 6.1 mmol/L (110 mg/dl) to 5.6 mmol/L (100 mg/dl) (6) in order to capture more individuals with IGT without performing an OGTT. The sensitivity for identifying IGT was increased with the new lower criterion for fasting glucose, but it also resulted in a two- to four fold increase in the prevalence of IFG across countries (7). Furthermore, with the lower cut-off, the overall incidence rate for diabetes among people with IFG was greatly reduced (8). This observation together with a lack of evidence for a reduction in adverse outcomes among these newly defined individuals with IFG, have led the WHO not to adopt the lower cut-off for IFG (3).

More recently, HbA_{1c} was recommended for the diagnosis of diabetes by both ADA and WHO (9, 10). However, in terms of identifying individuals with pre-diabetes or intermediate hyperglycaemia, the two organisations again differed in their recommendations. While ADA now recommends using HbA_{1c} in the range of 5.7-6.4% (39-47 mmol/mol) for defining pre-diabetes, WHO has not yet adopted HbA_{1c} for diagnosing intermediate hyperglycaemia/pre-

diabetes (9). The International Expert Committee (IEC), in turn, acknowledges the elevated risk of progression to diabetes associated with increasing HbA_{1c} levels and recommends initiation of prevention strategies in individuals with HbA_{1c} levels in a narrower range of 6.0-6.4% (42-47 mmol/mol) (11).

In addition to increasing risk of diabetes, both fasting glucose and HbA_{1c} levels in the range of pre-diabetes are associated with increased risk of cardiovascular disease (CVD) and mortality (12, 13). However, large inconsistencies between studies have been observed due to the use of different cut-points and reference groups (14), and direct comparisons between the associations of different glucose and HbA_{1c} criteria with development of CVD and/or mortality within the same population are sparse (15) . In the ongoing Whitehall II study we therefore compared the risk of fatal or non-fatal CVD or all-cause mortality in individuals with pre-diabetes identified by FPG, 2hPG or HbA_{1c} using the cut-points suggested by ADA versus WHO/IEC. Additionally, we examined the associations of continuous pre-diabetic levels of FPG, 2hPG or HbA_{1c} with the 10-year risk of CVD or mortality.

Research Design and Methods

Study Design and Participants

The prospective cohort study is based on participants from the Whitehall II study, which is an occupational cohort of 10,308 British civil servants (6,896 men, 3,412 women) initially recruited in 1985. The study population has been followed with clinical examinations every five years. This study is based on phase 7 (2002-04) and phase 9 (2007-09) where FPG, 2hPG and HbA_{1c} were measured, excluding participants with known diabetes. The study population consists of the 5,427 participants with complete information on both HbA_{1c} and FPG (87% of them also had 2hPG measured). All the included participants had been fasting $\geq$8 hours.

Ethics

The University College London Ethics Committee reviewed and approved the study. Written informed consent was obtained from all participants at each study phase. The Whitehall II study is described in detail elsewhere (16, 17).

Definition of pre-diabetes

At each study phase the participants had a standard 75-g OGTT with measurement of plasma glucose in the fasting state and after 120 min. HbA_{1c} was also measured. Pre-diabetes was defined according to the WHO/IEC criteria as FPG 6.1-6.9 mmol/L and/or HbA_{1c} 6.0-6.4% (42-47 mmol/mol) and according to the ADA criteria as FPG 5.6-6.9 mmol/L and/or HbA_{1c} 5.7-6.4% (39-47 mmol/mol). For 2hPG, we defined pre-diabetes as 7.8-11.0 mmol/L according to the definition by WHO and ADA. Normoglycaemia was defined as values below the cut-points for pre-diabetes for each diagnostic criterion.

Assessment of clinical characteristics

At all clinical examinations, measurements of anthropometry and handling of blood samples were carried out according to standard protocols (16). Plasma glucose concentrations were measured by the glucose oxidase method (17). HbA_{1c} was measured in whole blood, drawn into EDTA Monovette tubes, using the validated (18) Tosoh G8 high performance ion exchange liquid chromatography platform (Tosoh Bioscience, Tessenderlo, Belgium). Information on medication, family history of diabetes, smoking and alcohol intake was obtained from questionnaire.

Outcome ascertainment

Outcome was defined as a composite endpoint of CVD or death. The participants' unique National Health Service (NHS) identification numbers were linked to the NHS Hospital Episode Statistics database (19). Incidence of CVD was assessed over the follow-up period from 2002-04 to end of follow-up (30th June 2015) and included fatal and non-fatal coronary heart disease (defined by the ICD-9 codes 410-414 or ICD-10 codes I20-25) and stroke. Non-fatal myocardial infarction was determined using data from questionnaires, study electrocardiograms (ECGs), hospital acute ECGs, cardiac enzymes, and physician records (16). In the definition of stroke, cases identified by self-report only were excluded. Stroke included first subarachnoid haemorrhage, cerebral infarction, intra-cerebral haemorrhage, not specified stroke (ICD-10 codes I60–I64), and transient cerebral ischaemic attacks (ICD-10 code G45). Cases of stroke were ascertained from participants' general practitioners, by information extracted from hospital medical records, or from the NHS Hospital Episode Statistics database. Cardiovascular event ascertainment in the Whitehall II study has recently been validated (20). All-cause mortality was assessed from 2002-04 to end of follow-up by flagging participants at the NHS Central Registry, which provided information on the cause and date death.

Statistical analysis

Participants were followed from the date of their 2002-04 (or 2007-09) clinical examination until first registered event or to the end of follow-up (30th June 2015). When relevant, pre-diabetes status was allowed to change from normoglycaemia in phase 7 (2002-04) to pre-diabetes in phase 9 (2007-09). Poisson regression analysis with log risk time as offset was used to estimate crude incidence rates of an event and adjusted incidence rate ratios for subgroups of pre-diabetes defined by different criteria: WHO/IEC and ADA, and by different glycaemic measures (FPG, 2hPG and HbA_{1c}). Rate ratios were adjusted in a stepwise approach; first adjusting for age, sex and ethnicity, and secondly with further adjustment for previous CVD

and the CVD risk factors identified in the Framingham study (21): smoking, total cholesterol, HDL-cholesterol, systolic blood pressure, and use of antihypertensive treatment. To account for the non-constant effect of age over time on CVD risk and mortality, the follow-up period of each participant was split into 1-year age bands prior to analysis.

We performed two sensitivity analyses: 1) We repeated the analyses using only fatal and nonfatal CVD events as outcome (constituting 65% of the composite events) and censoring the study participants at time of death; 2) In a subset with complete information on FPG, HbA_{1c} and 2hPG levels (n=4,730), we expanded the analyses to include pre-diabetes by 2hPG (i.e. IGT).

We further calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the 10-year risk of an event for each pre-diabetes subgroup. We also estimated the 10-year risk of an event across the prediabetic range of glycaemia by the ADA criteria using Poisson regression analysis with models fitted separately for FPG, 2hPG and HbA_{1c}. In the models, the glycaemic measure was specified with natural cubic splines with three knots to facilitate detection of a potential inflection point in the associations.

Statistical analyses were performed in R version 3.2.3 (The R Foundation for Statistical Computing, www.R-project.org) and SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Pre-diabetes by different definitions

Using the WHO/IEC criteria, 402 (7.4%) of the 5,427 participants in the study population had pre-diabetes by the FPG criterion and 288 (5.3%) by the HbA_{1c} criterion (n=628 in total,

11.6%). Using the ADA criteria, 1,418 (26.1%) had pre-diabetes by FPG levels and 940 (17.3%) by HbA_{1c} (n=1,996 in total, 36.8%) (see *Supplementary Figure S1* for further details). Thus, the proportion of individuals with pre-diabetes was more than 3-fold higher using the ADA criterion compared to the WHO/IEC criterion. Applying the ADA criteria in the subset of the 4,730 individuals with full data on FPG, 2hPG and HbA_{1c}, 26.6% had pre-diabetes by FPG, 15.8% by HbA_{1c} and 14.2% by 2hPG.

For both WHO/IEC- and ADA-defined pre-diabetes, individuals identified by FPG levels only were more likely to be men and to report a higher amount of alcohol consumption than those identified by HbA_{1c} (*Table 1*). Those identified by HbA_{1c} only were more likely to be of non-White ethnicity, they were older, and had lower levels of total cholesterol, LDL cholesterol, and blood pressure than those identified by FPG levels only. However, those identified by HbA_{1c} were more likely to have had a previous CVD event and to be in antihypertensive- and/or lipid-lowering treatment (*Tables 1*).

Event rates in individuals with pre-diabetes by different definitions

Overall event rates: Median (IQR) follow-up time for a CVD or mortality event was 11.5 (8.9;12.1) years. During follow-up, 134 (21.3%) individuals with pre-diabetes by WHO/IEC FPG or HbA_{1c} criteria developed CVD or died. The corresponding number was 370 (18.5%) in the ADA pre-diabetes group. With the WHO/IEC criteria, the incidence rate of an event in those with pre-diabetes was 22.7 per 1000-PY which was 54% higher than in individuals with normoglycaemia (*Table 2*). The higher incidence rate in the pre-diabetes group was stable towards adjustment for age, sex and ethnicity, but decreased to 17% and became non-significant after adjustment for previous CVD, smoking, total cholesterol, HDL-cholesterol, systolic blood pressure, and use of antihypertensive treatment. Using the ADA criteria, the incidence rate for

the prediabetic group was somewhat lower at 18.9 per 1000-PY, which was 37% higher compared with the normoglycaemic group, and decreasing to only 12% higher (non-significant) in the fully adjusted model (*Table 2*).

Event rates by glycaemic criteria: Kaplan-Meier survival curves for an event for individuals with pre-diabetes versus normoglycaemia by different glycaemic criteria are shown in *Figure 1*, whereas rates and rate ratios are shown in *Table 1*. In individuals defined as having pre-diabetes by FPG levels (without taking the HbA_{1c} level into account), the rate of an event was 19.4 for FPG levels 6.1-6.9 mmol/L (WHO criteria) and 16.5 for FPG levels 5.6-6.9 mmol/L (ADA criteria) (*Figure 1A* and *Table 2*). In the fully adjusted model, the incidence rates were at the same level as that of the normoglycaemic group for both the WHO and ADA criteria (*Table 2*).

Among individuals with pre-diabetes by HbA_{1c} levels (without taking the FPG level into account), the incidence rate was 29.5 for HbA_{1c} levels 6.0-6.4% (IEC criteria) and 26.0 for HbA_{1c} levels 5.7-6.4% (ADA criteria) (*Figure 1B* and *Table 2*), which was around twice that of the rate in the normoglycaemic group for both the WHO and ADA criteria. Adjustment for age, sex and ethnicity decreased the excess in incidence rate to around 50%, and additional adjustment reduced it further to an excess of 13-17% (non-significant) (*Table 2*).

Analyses limiting the outcome to only include CVD-related events confirmed the associations reported above (*Supplementary Table S1*).

In the sensitivity analysis including only individuals with 2hPG measurements, the rate for pre-diabetes by 2hPG was 19.3 which was 44% higher compared with the normoglycaemic group

(< 7.8 mmol/L). Upon confounder adjustment there was no excess risk associated with pre-diabetes (*Table 2* and *Supplementary Figure S2*).

Comparing event rates between non-overlapping groups: The incidence rate of an event in individuals with pre-diabetes by FPG levels 5.6-6.0 mmol/L but normal HbA_{1c} levels (< 5.7%) was low and comparable to that of the normoglycaemic group (FPG < 5.6 mmol/L and HbA_{1c} < 5.7%) (~13 per 1000-PY, *Supplementary Figure S3*). In contrast, the incidence rate in people with pre-diabetes by HbA_{1c} 5.7-5.9% but normal FPG (< 5.6 mmol/L) was twice as high at 26.0 per 1000-PY (*Supplementary Figure S3*). After adjustment for age, sex and ethnicity, the rate was still 64% (25;117) higher in the group with HbA_{1c} 5.7-5.9% but normal FPG (< 5.6 mmol/L) compared with the group with FPG levels 5.6-6.0 mmol/L but normal HbA_{1c} levels (< 5.9%). Further adjustment for previous CVD, smoking, total cholesterol, HDL-cholesterol, systolic blood pressure, and use of antihypertensive treatment reduced this to 33% (0;77, P=0.046).

Performance of the different glycaemic criteria

The sensitivity and PPV for the 10-year risk of an event were low for all the pre-diabetes subgroups (*Supplementary Table S2*). Using the ADA criteria for FPG and HbA_{1c} more than doubled the sensitivity but decreased the specificity compared to the WHO/IEC criteria. The PPV was higher for pre-diabetes defined by HbA_{1c} than by FPG or 2hPG, whereas the NPV was similar across all the pre-diabetes subgroups.

Exploring event rates by increasing levels of glycaemia

The 10-year absolute risk of an event across the pre-diabetic range by the ADA criteria for FPG, 2hPG and HbA_{1c} is shown in *Figure 2*. The risk was higher for all levels of HbA_{1c}, whereas for FPG and 2hPG the risk across the pre-diabetic range was somewhat comparable. There was no indication of an inflection point for any of the glycaemic measures.

Conclusions

In the present large prospective Whitehall II cohort study of adults aged 50-80 years with simultaneous measures of different glycaemic measures, we found that the prevalence of pre-diabetes defined by FPG and/or HbA_{1c} was three times higher when the ADA criteria were used compared with the WHO/IEC definitions. Individuals with pre-diabetes defined by HbA_{1c} had substantially higher risk of CVD and mortality than those defined by the FPG or 2hPG criteria irrespective of whether the cut-point of 5.7% (39 mmol/mol) or 6.0% (42 mmol/mol) was used. For none of the glycaemic measures did we find an inflection point for risk of CVD and mortality over the pre-diabetic range. Furthermore, the excess risk of CVD and death associated with having pre-diabetes was greatly reduced in HbA_{1c}-defined pre-diabetes and null in FPG- and 2hPG-defined pre-diabetes after adjustment for demographic and cardiovascular risk factors. These findings indicate that there is no obvious optimal glycaemic cut-off for risk stratification, and the higher risk for CVD and death among individuals with pre-diabetes is mainly explained by its clustering with other risk factors associated with hyperglycaemia. This challenges the use of the pre-diabetes classification as a stand-alone tool for risk stratification among older adults.

Only a few previous studies have compared different definitions of pre-diabetes in relation to CVD and mortality in the same population (15, 22). Warren et al. found in the prospective Atherosclerosis Risk in Communities (ARIC) study that HbA_{1c} was more specific and provided

better risk discriminating regarding future major events than FPG or 2hPG concentrations. After adjustment for cardiovascular risk factors, the risk of all-cause mortality was reduced but still significantly elevated in those with HbA_{1c}-defined pre-diabetes. However, incidence rates for cardiovascular mortality became non-significant for all pre-diabetic subgroups after adjustment for cardiovascular risk factors (15), which is in accordance with the findings from our analysis and underscores the importance of focusing on non-glycaemic risk factors in individuals with pre-diabetes. In contrast to the ARIC study, we also reported absolute 10-year risk estimates over the pre-diabetic range of all the three glycaemic measures, and these showed a higher absolute risk for HbA_{1c} than for FPG and 2hPG concentrations. We found no inflection point of risk in the association which is in line with the findings from the population-based Australian Diabetes, Obesity and Lifestyle (AusDiab) study (13). Secondly, we evaluated the risk associated with different combinations of HbA_{1c} and FPG levels, which enabled us to show that pre-diabetic HbA_{1c} levels are associated with elevated risk of CVD and death even when FPG levels are normal, while the opposite is not the case (i.e. pre-diabetic FPG and normal HbA_{1c} levels). In support of this finding, data from the ADDITION study showed that among individuals with normal glucose tolerance on an OGTT, those with HbA_{1c} levels in the range 6.0-6.4% had 21% higher risk of all-cause mortality than those with HbA_{1c} levels < 6.0% (23), again suggesting that HbA_{1c} predicts mortality beyond fasting and 2-hour glucose levels. In relation to the use of FPG for diagnosis of pre-diabetes, results from meta-analyses have shown that pre-diabetes defined by the WHO IFG criterion, but not the ADA IFG criterion, is associated with increased risk of cardiovascular and all-cause mortality (24). Similar results were found in relation to the risk of stroke (25). A recent meta-analysis, however, concluded that IFG defined by the ADA criterion is associated with an increased risk of all-cause mortality, cardiovascular mortality, coronary heart disease and stroke (14). However, a subgroup analysis revealed that among individuals aged 55 years or above ADA-defined IFG was not associated

with all-cause mortality (14). Combined with our results these findings suggest that the increased CVD and mortality risk associated with pre-diabetic FPG levels may decrease with age. It is thus likely that FPG is better for risk stratification in younger adults, whereas HbA_{1c} is a better and more stable measure for health status in older adults, but this hypothesis needs to be tested in study populations with a wide age range. Part of the stronger association found between HbA_{1c} and incident CVD may be explained by its capacity to reflect average glycaemia, but HbA_{1c} may also indirectly capture information about other important pathophysiological processes such as iron metabolism and low-grade inflammation (26, 27). However, their causal effects need to be examined in more detail.

A major strength of the Whitehall II cohort is that the measures of FPG, 2hPG and HbA_{1c} were obtained simultaneously and can be linked to validated measures of morbidity and mortality over a long follow-up period (20). Deaths attributable to other causes than CVD were included in the analysis to avoid bias from competing risk. However, two out of three of the composite events were related to CVD, and sensitivity analyses with only CVD as outcome were consistent with our conclusions. Another strength of the current analysis is the application of all the different definitions for pre-diabetes. Most previous studies have only focused on a single definition of pre-diabetes (either WHO/IEC or ADA) and thereby used different reference groups for defining normoglycaemia (13, 23, 28). Accordingly, event rates cannot be compared directly across studies to derive solid evidence on the association of pre-diabetes with morbidity and mortality. This could also explain why previous meta-analyses on the relationship of pre-diabetes with future morbidity and mortality have shown conflicting results (12, 13, 24, 25). In the Whitehall II study, some individuals with pre-diabetes may develop diabetes during follow-up and subsequently receive treatment to reduce CVD risk. This could potentially have biased the results in the sense that the calculated event rates for WHO/IEC defined pre-diabetes are

underestimated relative to the rates in ADA defined pre-diabetes, which have lower levels of glycaemia and therefore are less likely to convert to diabetes during follow-up. It is also possible that the way diabetes has been diagnosed by general practitioners between the study visits during follow up may have introduced bias. Before 2012, diabetes was mostly diagnosed by measurement of FPG levels, but after 2012 there has been a shift from FPG to HbA_{1c} for diagnosis of diabetes in clinical practice in the UK (9). However, given that end of follow-up in our study was 30th June 2015, we expect these effects to even out. Therefore, it is reasonable to believe that the differential associations of FPG versus HbA_{1c} with CVD and mortality are not caused by diagnosis and treatment of diabetes and CVD risk in individuals identified by one specific diagnostic criterion over another during follow-up.

During the last decades there has been an increased focus on identifying high-risk individuals in order to prevent future disease and premature mortality. As a result, the diagnostic thresholds have been lowered for many diseases (29), which has increased sensitivity at the cost of specificity. With the adoption of HbA_{1c} as a diagnostic criterion for diabetes (9, 30), the possibility of also using HbA_{1c} to risk-stratify individuals for diabetes prevention is obvious, but the challenge is to choose the optimal cut-point. As shown in this and other studies (13, 28), there does not seem to be an inflection point in the non-diabetic range for HbA_{1c} in the association with CVD or mortality. Accordingly, when deciding on the diagnostic test and thresholds used to guide preventive interventions one needs to consider the effectiveness of interventions as well as the health and economic consequences of false-positives and false-negatives (5, 31). The major diabetes prevention trials performed so far have included individuals with IGT and not people identified as having high risk by FPG or HbA_{1c} (32-34). Despite the limited evidence for prevention in these groups of individuals, the current recommendations from ADA suggest that all individuals with pre-diabetes (IFG, IGT and/or

HbA_{1c} 5.7-6.4%) should be targeted for diabetes preventive efforts (lifestyle modification or metformin) (35). Because of the poor concordance between the different diagnostic criteria, it is questionable whether results from trials in IGT will apply to individuals identified by slightly elevated FPG or HbA_{1c} levels. Thus, intervention studies among individuals identified by FPG or HbA_{1c} aiming at reducing risk for diabetes and CVD are warranted in order to improve and modify the current recommendations (36). More recent research also suggests that intermediate time points or different glucose curve patterns during an OGTT may be relevant to use for risk stratification purposes (37, 38). Lastly, it will be important to evaluate pre-diabetes in the context of overall CVD risk, because of the close relationship of glycaemia with other cardiovascular risk factors. Thus, future risk prediction models should study whether easily measured risk factors and/or cheap biomarkers can jointly predict future diabetes, CVD and mortality.

In conclusion, our study showed that individuals with pre-diabetes defined using the ADA criteria have a lower risk of CVD and all-cause mortality than pre-diabetic individuals identified by the WHO/IEC criteria. This difference was mainly driven by the lower incidence of CVD or death among individuals with impaired fasting glucose but normal levels of HbA_{1c}. Our results showed a high incidence rate of CVD and death in those with HbA_{1c} levels 5.7-5.9%, which advocates for lowering the cut-point for pre-diabetes below that of 6.0% for CVD preventive interventions. That said, our study also shows that a substantial part of the excess risk in pre-diabetes is explained by other CVD risk factors, suggesting that the use of pre-diabetes as an independent factor for risk stratification is questionable.

Author contributions

Dorte Vistisen and Kristine Færch contributed to the study concept and design, planned the statistical analyses, and drafted the manuscript. Dorte Vistisen conducted the statistical analysis. Eric Brunner, Mika Kivimäki and Adam Tabák provided data. All authors provided intellectual input and read and approved the final version of the manuscript. Dorte Vistisen and Kristine Færch are guarantors of the contents of the article.

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Role of the funding source

The funders of the study had no role in study design, data collection, analysis, interpretation, or writing of the report. Dorte Vistisen and Kristine Færch had full access to all the study data and had final responsibility for the decision to submit for publication.

Disclosures

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Data sharing

Whitehall II data, protocols, and other metadata are available to the scientific community. Please refer to the Whitehall II data sharing policy at https://www.ucl.ac.uk/whitehallII/data-sharing.

Figure 1 Kaplan-Meier survival curves for an event (cardiovascular disease or mortality) for individuals with pre-diabetes (light blue and dark blue) versus normal glycaemia (grey), using fasting plasma glucose, n=5,427 (A), HbA_{1c}, n=5,427 (B) or 2-hour glucose, n=4,730 (C). FPG: Fasting plasma glucose; 2hPG: 2-hour plasma glucose.

Figure 2 Association between glycaemia and 10-year risk of an event (cardiovascular disease or mortality) in the pre-diabetic range. FPG: Fasting plasma glucose; 2hPG: 2-hour plasma glucose.

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Table 1 Baseline characteristics by normal glycaemia and subgroups of pre-diabetes defined by WHO/International Expert Committee and ADA

		Pre-diabetes			
	Normal glycaemia	**FPG only**	**HbA_{1c} only**	**Both**	**P**
WHO/IEC					
N	4799	340	226	62	
Men (%)	71.6 (70.3;72.9)	85.6 (81.4;89.1) [a]	67.3 (60.7;73.3) [b]	66.1 (53.0;77.7) [b]	<0.001
White ethnicity (%)	93.6 (92.9;94.3)	90.6 (87.0;93.5) [a]	80.1 (74.3;85.1) [a,b]	83.9 (72.3;92.0) [a]	<0.001
Age (years)	61.2 (6.1)	61.8 (6.1)	65.5 (6.4) [a,b]	64.2 (5.7) [a,b]	<0.001
BMI (kg/m^2)	26.4 (4.1)	28.2 (4.4) [a]	27.7 (4.7) [a]	30.4 (6.2) [a,b,c]	<0.001
Total cholesterol (mmol/l)	5.7 (1.0)	5.7 (1.0)	5.3 (1.1) [a,b]	5.6 (1.3)	<0.001
HDL cholesterol (mmol(l)	1.6 (0.4)	1.5 (0.5) [a]	1.5 (0.4) [a]	1.4 (0.3) [a]	<0.001
Systolic blood pressure (mmHg)	126.6 (16.2)	134.4 (17.3) [a]	128.5 (17.8) [b]	136.9 (19.3) [a,c]	<0.001
Fasting plasma glucose (mmol/L)	5.2 (0.4)	6.3 (0.2) [a]	5.5 (0.9) [a,b]	6.4 (0.2) [a,c]	<0.001
2-hour plasma glucose (mmol/L)	6.1 (1.5)	7.4 (2.0) [a]	7.5 (2.5) [a]	9.5 (2.3) [a,b,c]	<0.001
HbA_{1c} (%)	5.2 (0.4)	5.5 (0.5) [a]	6.1 (0.1) [a,b]	6.1 (0.1) [a,b]	<0.001
HbA_{1c} (mmol/mol)	34 (4)	37 (5) [a]	43 (1) [a,b]	44 (2) [a,b]	<0.001
Previous cardiovascular disease (%)	9.7 (8.9;10.6)	12.1 (8.8;16.0)	18.1 (13.3;23.8) [a,b]	24.2 (14.2;36.7) [a,b]	<0.001
Current smoker (%)	7.9 (7.2;8.7)	5.9 (3.6;8.9)	10.2 (6.6;14.9)	9.7 (3.6;19.9)	0.282
Antihypertensive treatment (%)	21.9 (20.7;23.1)	36.2 (31.1;41.5) [a]	42.0 (35.5;48.8) [a]	45.2 (32.5;58.3) [a]	<0.001
ADA					
N	3431	1056	578	362	
Men (%)	69.4 (67.8;70.9)	83.9 (81.5;86.1) [a]	66.8 (62.8;70.6) [b]	75.1 (70.4;79.5) [a,b,c]	<0.001
White ethnicity (%)	94.3 (93.5;95.1)	94.5 (93.0;95.8)	83.4 (80.1;86.3) [a,b]	87.0 (83.1;90.3) [a,c]	<0.001
Age (years)	60.8 (6.0)	61.1 (6.0)	64.8 (6.6) [a,b]	63.6 (6.1) [a,b,c]	<0.001
BMI (kg/m^2)	26.1 (4.1)	27.4 (4.2) [a]	27.2 (4.5) [a]	28.5 (4.5) [a,b,c]	<0.001
Total cholesterol (mmol/l)	5.7 (1.0)	5.8 (1.0)	5.5 (1.1) [a,b]	5.6 (1.2) [b]	<0.001
HDL cholesterol (mmol(l)	1.6 (0.5)	1.5 (0.4) [a]	1.6 (0.4) [a]	1.5 (0.4) [a,b,c]	<0.001
Systolic blood pressure (mmHg)	125.7 (16.2)	130.9 (16.5) [a]	127.3 (16.9) [a,b]	131.2 (16.6) [a,c]	<0.001

Fasting plasma glucose (mmol/L)	5.0 (0.3)	5.9 (0.3) [a]	5.2 (0.7) [a,b]	6.0 (0.3) [a,b,a]	<0.001
2-hour plasma glucose (mmol/L)	5.9 (1.5)	6.5 (1.7) [a]	6.7 (2.1) [a]	7.8 (2.1) [a,b,c]	<0.001
HbA_{1c} (%)	5.1 (0.3)	5.3 (0.4) [a]	5.9 (0.2) [a,b]	5.9 (0.2) [a,b]	<0.001
HbA_{1c} (mmol/mol)	33 (3)	34 (4) [a]	41 (2) [a,b]	41 (2) [a,b]	<0.001
Previous cardiovascular disease (%)	9.5 (8.5;10.5)	10.5 (8.7;12.5)	18.0 (14.9;21.4) [a,b]	19.9 (15.9;24.4) [a,b]	<0.001
Current smoker (%)	8.0 (7.1;8.9)	6.8 (5.4;8.5)	9.3 (7.1;12.0)	8.6 (5.9;11.9)	0.312
Antihypertensive treatment (%)	19.5 (18.2;20.9)	27.1 (24.4;29.9) [a]	33.7 (29.9;37.8) [a,b]	41.7 (36.6;47.0) [a,b,c]	<0.001

Data are means (SD), medians (interquartile range) or proportions (95% CI).

WHO/IEC: Normal glycaemia: FPG < 6.1 mmol/L and HbA_{1c} < 6.0%; FPG only: FPG 6.1-6.9 mmol/L and HbA_{1c} < 6.0%; HbA_{1c} only: HbA_{1c} < 6.0-6.4% and FPG <6.1 mmol/L; Both: FPG 6.1-6.9 mmol/L and HbA_{1c} 6.0-6.4%.

ADA: Normal glycaemia: FPG < 5.6 mmol/L and HbA_{1c} < 5.7%; FPG only: FPG 5.6-6.9 mmol/L and HbA_{1c} < 5.7%; HbA_{1c} only: HbA_{1c} < 5.7-6.4% and FPG <5.6 mmol/L; Both: FPG 5.6-6.9 mmol/L and HbA_{1c} 5.7-6.4%.

P is the level of significance for the overall unadjusted test of difference between groups of normal glycaemia and pre-diabetes subgroups, using t-tests for difference in means or log(means) and chi-square tests for difference in proportions. [a] vs NGT, P < 0.05; [b] vs FPG only, P < 0.05; [c] vs HbA_{1c} only, P < 0.05

Table 2 Rates and rate ratios of an event (cardiovascular disease or mortality) for pre-diabetes subgroups, using the WHO/IEC criteria or the ADA criteria.

WHO/IEC	**Definition**	**Rate per 1000-PY**	**RR**	**RR_{adj1}**	**RR_{adj2}**
Overall					
Normal glycaemia	FPG < 6.1 mmol/L and HbA_{1c} < 6.0%	14.8 (13.7;15.9)	ref	ref	ref
Pre-diabetes	FPG 6.1-6.9 mmol/L or HbA_{1c} 6.0-6.4%	22.7 (19.2;26.9)	1.54 (1.28;1.85)	1.51 (1.25;1.81)	1.17 (0.97;1.41)
By HbA_{1c}					
Normal glycaemia	HbA_{1c} < 6.0%	14.9 (13.9; 15.9)	ref	ref	ref
Pre-diabetes	HbA_{1c} 6.0-6.4%	29.5 (23.4; 37.3)	1.99 (1.55;2.53)	1.52 (1.19;1.95)	1.13 (0.88;1.46)
By FPG					
Normal glycaemia	FPG < 6.1 mmol/L	15.3 (14.2;16.4)	ref	ref	ref
Pre-diabetes	FPG 6.1-6.9 mmol/L	19.4 (15.6;24.2)	1.27 (1.01;1.60)	1.17 (0.93;1.48)	1.00 (0.79;1.26)
By 2hPG					
Normal glycaemia	2hPG < 7.8 mmol/L	13.4 (12.4;14.6)	ref	ref	ref
Pre-diabetes	2hPG 7.8-11.0 mmol/L	19.3 (16.3;23.0)	1.44 (1.19;1.75)	1.14 (0.94;1.39)	1.00 (0.82; 1.22)
ADA					

Overall					
Normal glycaemia	FPG < 5.6 mmol/L and HbA_{1c} < 5.7%	13.8 (12.7;15. 1)	ref	ref	ref
Pre-diabetes	FPG 5.6-6.9 mmol/L or HbA_{1c} 5.7-6.4%	18.9 (17.1;21.0)	1.37 (1.20;1.57)	1.34 (1.17; 1.54)	1.12 (0.97;1.28)
By HbA_{1c}					
Normal glycaemia	HbA_{1c} < 5.7%	13.7 (12.7;14.8)	ref	ref	ref
Pre-diabetes	HbA_{1c} 5.7-6.4%	26.0 (22.6;29.8)	1.89 (1.62;2.22)	1.49 (1.27;1.75)	1.17 (1.00;1.38)
	HbA_{1c} 5.7-5.9%	24.6 (20.8;29.0)	1.79 (1.50;2.15)	1.43 (1.19;1.72)	1.18 (0.98; 1.42)
	HbA_{1c} 6.0-6.4%	29.5 (23.4;37.3)	2.15 (1.68;2.76)	1.62 (1.26;2.08)	1.13 (0.87; 1.46)
By FPG					
Normal glycaemia	FPG < 5.6 mmol/L	15.2 (14.1;16.5)	ref	ref	ref
Pre-diabetes	FPG 5.6-6.9 mmol/L	16.5 (14.5;18.7)	1.08 (0.93;1.25)	1.00 (0.86;1.16)	0.93 (0.80;1.08)
	FPG 5.6-6.0 mmol/L	15.4 (13.2;17.9)	1.01 (0.85;1.20)	0.94 (0.79;1.12)	0.91 (0.76; 1.08)
	FPG 6.1-6.9 mmol/L	19.4 (15.6;24.2)	1.27 (1.01;1.61)	1.16 (0.91;1.46)	0.98 (0.77; 1.24)
By 2hPG					
Normal glycaemia	2hPG < 7.8 mmol/L	13.4 (12.4;14.6)	ref	ref	ref
Pre-diabetes	2hPG 7.8-11.0 mmol/L	19.3 (16.3;23.0)	1.44 (1.19;1.75)	1.14 (0.94;1.39)	1.00 (0.82; 1.22)

IEC: International Expert Committee; FPG: fasting plasma glucose; 2hPG: 2-hour plasma glucose; RR: crude rate ratio; RR_{adj1}: rate ratio adjusted for age, sex and ethnicity; RR_{adj2}: rate ratio adjusted for age, sex, ethnicity, previous CVD, smoking, total cholesterol, HDL-cholesterol, systolic blood pressure, and use of antihypertensive treatment