Trajectories of cardiometabolic risk factors before diagnosis of three subtypes of type 2 diabetes: a post-hoc analysis of the longitudinal Whitehall II cohort study

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Summary

Background Most clinicians acknowledge that type 2 diabetes is multifactorial and has heterogeneous characteristics, but neither prevention nor treatment is systematically stratified. To address the heterogeneity of the disease, we examined whether patients diagnosed on the basis of fasting glucose concentrations, those diagnosed on the basis of 2 h concentrations, and those diagnosed on the basis of both criteria differed in terms of pathogenesis or cardiovascular risks.

Methods Retrospectively, we analysed trajectories of cardiometabolic risk factors and 10 year cardiovascular risks in the prospective Whitehall II study cohort by use of multilevel longitudinal modelling. Participants were diagnosed by 75 g oral glucose-tolerance tests. We classified those diagnosed with type 2 diabetes into three subgroups: diagnosed on the basis of fasting glucose concentrations, diagnosed on the basis of 2 h glucose concentrations, and diagnosed on the basis of both concentrations. We also developed a classification tree for identification of individuals who are likely to have high fasting and 2 h glucose concentrations, but for whom only fasting concentrations are available.

Results Median follow-up was 14·2 years with 15 826 person-examinations (1991–2009). Of 10 308 individuals, 6843 were included and 6569 remained diabetes free. 274 cases of type 2 diabetes were identified: 55 had high fasting glucose concentrations only, 148 had high 2 h concentrations only, and 71 had high fasting and 2 h concentrations. At diagnosis, participants with high fasting and 2 h glucose concentrations had higher mean body-mass indices (30·9 kg/m^2 [SD 5·7]) than did those with high fasting concentrations (28·4 kg/m^2 [4·4]; p=0·0009) or 2 h concentrations (27·9 kg/m^2 [4·9]; <0·0001). Mean glycated haemoglobin A_{1c} concentrations were also higher in the fasting and 2 h subgroup (7·4% [1·6]) than in the fasting (5·9% [0·5]; <0·0001) or 2 h (5·9% [0·6]; <0·0001) sugroups. Additionally, the fasting and 2 h subgroup had a higher proportion of individuals with moderate or high risk of cardiovascular disease than did the fasting subgroup (p=0·02). A classic pattern of β-cell decompensation before diagnosis was noted only in the fasting and 2 h subgroup. Additionally, glucose concentrations and insulin resistance accelerated more substantially before diagnosis in the fasting and 2 h subgroup than in the fasting subgroup or the 2 h subgroup.

Interpretation Patients with type 2 diabetes diagnosed on the basis of increased fasting glucose concentrations or 2 h glucose concentrations, or both, have distinct cardiometabolic risk development before diagnosis.

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Introduction

Type 2 diabetes is defined as a single disease entity irrespective of the way in which it is diagnosed. Even though most clinicians recognise that the disease is multifactorial and has heterogeneous characteristics, stratification of prevention or treatment is not done systematically.

As type 2 diabetes develops, the blood glucose rises from normoglycaemia to a slightly increased concentration (ie, prediabetic state) and finally to a hyperglycaemic state that exceeds the diagnostic criteria for the illness. Previous longitudinal analyses[1] from the Whitehall II study have shown that fasting and 2 h postload glucose concentrations increase at different timepoints in the years preceding diagnosis of type 2 diabetes, suggesting possible differences in disease development. Individuals with prediabetes in whom only fasting plasma glucose concentrations are raised are phenotypically different from those with increased 2 h glucose concentrations only.[2–4] Individuals in whom both fasting and 2 h glucose concentrations are raised have a worse risk profile[3,4] and a higher risk of progression to type 2 diabetes[5] than do those with isolated fasting or 2 h hyperglycaemia. The major pathophysiological drivers in the different prediabetic states probably continue to operate when fasting or 2 h glucose concentrations further rise into the diabetic range, implying that stratified prevention and possibly stratified treatment might be beneficial. In this longitudinal cohort study, we established 18 year trajectories of traditional cardiometabolic risk factors preceding diagnosis of type 2

diabetes based on fasting glucose or 2 h glucose concentrations, or both. We also developed a model to identify the individuals who are likely to have high fasting and 2 h glucose concentrations, but for whom only fasting concentrations are available.

Methods

Study design and participants

Whitehall II was a longitudinal study of a cohort of non-industrial UK civil servants and has been previously described in detail.[6] Its original aim was to investigate the importance of stress and social class for cardiovascular health. 10 308 participants (6896 [66·9%] of whom were male) who worked in the London offices of 20 departments and were aged 35–55 years were recruited between August, 1985, and April, 1988 (phase 1), and followed up in eight subsequent phases roughly 2·5 years apart. A questionnaire was administered in all phases, and every second phase (ie, phases 1, 3, 5, 7, and 9) additionally included a clinical health examination. The numbers of participants in these subsequent clinical phases, which were defined as the numbers who either returned a questionnaire or attended a clinical examination, were 6057 men and 2758 women in phase 3 (1991–93), 5473 men and 2397 women in phase 5 (1997–99), 4893 men and 2074 women in phase 7 (2002–04), and 4759 men and 2002 women in phase 9 (2007–09). The Whitehall II study was reviewed and approved by the University College London

	Diabetes based on fasting glucose (n=55)	Diabetes based on 2 h glucose (n=148)	Diabetes based on fasting and 2 glucose (n=71)	Participants without diabetes (n=6569)
Men	44 (80·0%)	107 (72·3%)	57 (80·3%)	4618 (70·3%)
Age (years)	60·0 (6·9)	63·0 (6·6)*	60·8 (6·0)	60·4 (7·9)†
White ethnic origin	43 (78·2%)	125 (84·5%)	53 (74·6%)	6063 (92·3%)‡
Current smoker	2 (3·6%)	11 (7·4%)	10 (14·1%)	650 (9·9%)
Family history of diabetes mellitus	13 (23·6%)	33 (22·3%)	17 (23·9%)	617 (9·4%)‡
10 year cardiovascular disease risk ≥15%	22 (40·0%)	70 (47·3%)	43 (60·6%)*	434 (6·6%)‡
Antihypertensive treatment	19 (34·5%)	58 (39·2%)	22 (31·0%)	1478 (22·5%)†
Lipid-lowering treatment	11 (20·0%)	34 (23·0%)	11 (15·5%)	1031 (15·7%)†
Fasting plasma glucose (mmol/L)	7·3 (0·5)	5·8 (0·7)*	9·1 (2·7)§	5·2 (0·5)‡
2 h plasma glucose (mmol/L)	8·2 (2·0)	12·2 (1·0)*	15·5 (4·0)§	6·0 (1·6)‡
HbA_{1c}				
%	5·9 (0·5)	5·9 (0·6)	7·4 (1·6)§	5·5 (0·4)‡
mmol/mol	41 (5·7)	41 (6·5)	57 (17·7) §	37 (4·6)‡
Body-mass index (kg/m^2)	28·4 (4·4)	27·9 (4·9)	30·9 (5·7)§	26·2 (4·1)‡
Waist circumference (cm)	100·0 (12·5)	97·5 (12·1)	104·4 (11·4)†	91·8 (12·2)‡
Hip circumference (cm)	102·8 (8·9)	101·6 (9·0)	105·2 (11·3)†	99·8 (7·9)‡
Waist–hip ratio	0·97 (0·07)	0·96 (0·07)	1·00 (0·07)†	0·92 (0·08)‡
Height (m)	172·2 (9·9)	168·9 (9·3)*	171·4 (8·0)	171·4 (9·2)†
Total cholesterol (mmol/L)	5·8 (1·2)	5·7 (1·1)	5·9 (1·0)	5·7 (1·2)
HDL cholesterol (mmol/L)	1·4 (0·3)	1·5 (0·4)	1·2 (0·3)†	1·6 (0·4)¶
LDL cholesterol (mmol/L)	3·7 (1·2)	3·5 (1·0)	3·7 (0·9)	3·6 (1·1)
Triglycerides (mmol/L)	1·6 (0·8)	1·5 (0·8)	2·0 (1·0)§	1·3 (0·8)‡
Adiponectin (μg/mL)‖	6·5 (6·4–11·3)	6·4 (5·1–8·8)	4·9 (3·3–8·7)	8·7 (6·3–13·2)**
Systolic blood pressure (mm Hg)	127·9 (17·5)	132·6 (18·4)	138·3 (17·9)§	124·0 (15·6)**
Diastolic blood pressure (mm Hg)	75·3 (11·1)	77·6 (12·2)	83·1 (12·9)§	74·2 (10·8)**
Fasting insulin (pmol/L)	14·7 (8·6–22·1)	10·6 (6·7–16·3)*	17·0 (10·5–22·1)†	6·6 (4·4–9·9)‡
2 h insulin (pmol/L)	57·5 (35·2–93·7)	88·7 (60·1–131·6)	50·4 (35·6–90·8)†	37·9 (23·2–62·9)‡
HOMA-insulin resistance	4·7 (3·0–6·8)	2·9 (1·8–4·6)*	6·2 (3·9–8·5)§	1·6 (1·1–2·4)‡
HOMA-β-cell function	77·1 (48·3–105·0)	95·7 (66·5–151·1)*	66·3 (37·0–100·0)†	86·3 (60·3–124·6)¶
Insulin sensitivity index (mg l^2/mmol mU min)	47·8 (36·9–65·6)	33·9 (28·3–41·4)*	31·8 (25·5–44·0)*	91·4 (61·7–150)‡

Data are n (%), mean (SD), or median (IQR). HOMA=homoeostasis model of assessment. To test differences in characteristics between subgroups, the χ^2 test was used for categorical variables, *t* test for normal continuous data, and Mann-Whitney *U* test for non-normal continuous data. Two-sided 5% level of significance adjusted for multiple testing with Benjamini et al's method.[33] *Significantly different from fasting subgroup. †Significantly different from 2 h subgroup. ‡Significantly different from fasting, 2 h, and fasting and 2 h subgroups. §Signicantly different from fasting subgroup and 2 h subgroup. ¶Significantly different from fasting subgroup and fasting and 2 h subgroup. ‖n=24 in the fasting subgroup, n=70 in the 2 h subgroup, n=36 in the fasting and 2 h subgroup, and n=2336 in the diabetes-free group. **Significantly different from 2 h subgroup and fasting and 2 h subgroup.

Table: **Characteristics of patients with type 2 diabetes diagnosed on the basis of fasting glucose concentrations or 2 h concentrations, or both, at time of diagnosis, and of those without diabetes at last clinical examination**

Ethics Committee (85/0938), and written informed consent was obtained from each participant at each phase. The study was done according to the principles of the Helsinki Declaration.

Procedures

We used phase 3—ie, when the oral glucose tolerance test (OGTT) was first done—as the baseline for our analysis, and final follow-up was the phase 9 examination. We excluded 1032 (10·0%) participants who were lost to follow-up before phase 3, 153 (1·5%) participants with prevalent diabetes before phase 3, and 1759 (17·1%) participants who fasted for less than 8 h before the clinical examination in all study phases. When fasting duration was less than 8 h in one phase, the participant was excluded from that phase only. 795 of the remaining 7364 (10·8%) participants developed type 2 diabetes during the study. However, because diagnosis with a full and valid OGTT was necessary,[7] we further excluded 358 (4·9%) patients whose type 2 diabetes was diagnosed by a doctor outside the study and 163 (2·3%) participants in whom the disorder was diagnosed by screening, but for whom data for both a valid fasting and 2 h glucose measurement were not available. Thus, our final sample was 6843 participants (66·4% of the original sample); median follow-up was 14·2 years (IQR 8·7–16·2), 15826 person-examinations were done, and 274 cases of type 2 diabetes were diagnosed by screen detection by phase 9. We classified these 274 cases into three subgroups—namely, cases diagnosed on the basis of fasting glucose only (ie, fasting glucose ≥7·0 mmol/L, 2 h glucose <11·1 mmol/L), those diagnosed on the basis of 2 h glucose only (ie, fasting glucose <7·0 mmol/L, 2 h glucose ≥11·1 mmol/L), and those diagnosed on the basis of both criteria (ie, fasting glucose ≥7·0 mmol/L, 2 h glucose ≥11·1 mmol/L). A flow diagram of the number of participants included at each phase is shown in the appendix.

Measurements

In phases 3, 5, 7, and 9 of Whitehall II, standard 2 h 75 g OGTTs were done in the morning after overnight fasting (≥8 h, estimated by the difference between self-reported time of most recent meal and the OGTT), or in the afternoon after no more than a light fat-free breakfast eaten before 0800 h (≥5 h of fasting).

Anthropometry was done and blood pressure measured according to standard protocols.[6] Data for ethnic origin, smoking status, and family history of diabetes (types 1 and 2) were gathered via a questionnaire. During all phases, blood samples were handled according to standardised procedures. Blood glucose was measured by the glucose oxidase method;[1] serum insulin by in-house radioimmunoassays;[8] and serum triglycerides, total cholesterol, and HDL cholesterol concentrations by automated enzymatic colorimetric methods. LDL cholesterol was calculated with the Friedewald formula, and serum adiponectin concentrations measured in 2466 (36·0%) participants with the Quantikine ELISA kit (R&D Systems, Wiesbaden, Germany).[9]

Statistical analysis

We used the homoeostasis model assessment (HOMA) to estimate insulin resistance and β-cell function,[10] the insulin sensitivity index to estimate whole-body insulin sensitivity,[11] and the Framingham cardiovascular disease risk score to calculate absolute 10 year risk of developing general cardiovascular disease.[12] We classified a risk score of 15% or greater as a moderate or high risk of cardiovascular disease.

The observation period for retrospective trajectories started at the date of diagnosis by OGTT for patients who developed type 2 diabetes, and at the last screening or questionnaire phase for those who did not develop the disorder (year 0). Trajectories of the following outcomes were followed back in time to the first clinical examination: fasting and 2 h plasma glucose concentrations; fasting and 2 h serum insulin concentrations; HOMA-β-cell function, HOMA-insulin resistance, and insulin sensitivity index; body-mass index and waist–hip ratio; systolic and diastolic blood pressure; total, HDL, and

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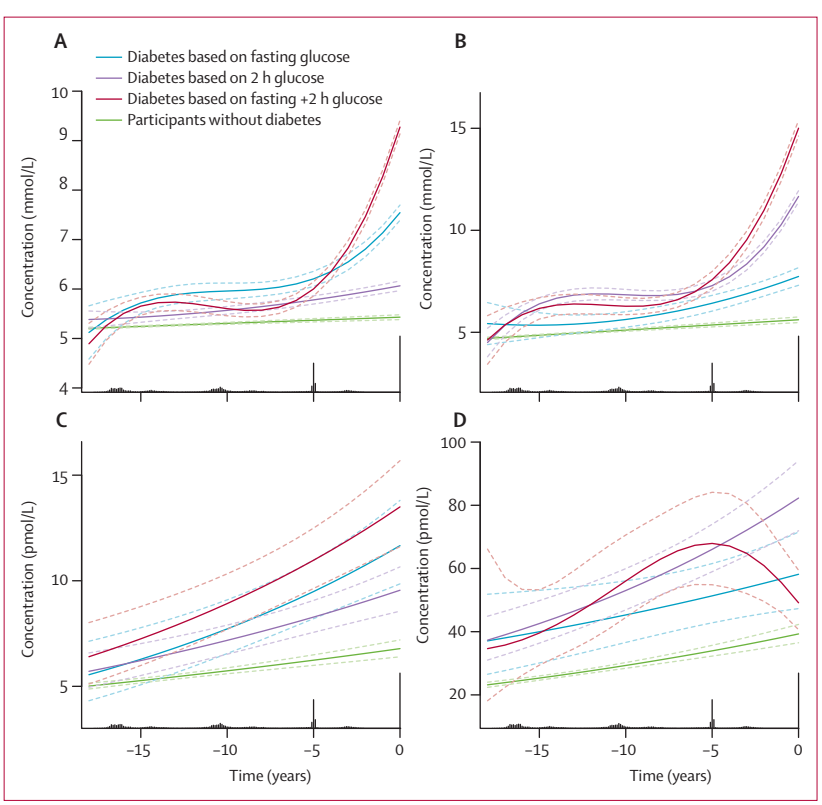

Figure 1: **Trajectories of fasting plasma glucose (A), 2 h plasma glucose (B), fasting serum insulin (C), and 2 h serum insulin (D) concentrations for a hypothetical, white, 60-year-old man (in year 0) from 18 years before diagnosis of type 2 diabetes or last clinical examination**

Time 0=diagnosis or last clinical examination. Solid lines are estimated trajectories and dashed lines are 95% CIs. Black bars show data distribution during follow-up.

LDL cholesterol concentrations; triglyceride concentrations; adiponectin concentrations; and the Framingham cardiovascular disease risk score. Before analysis, we log-transformed outcomes that did not follow a normal distribution (fasting and 2 h serum insulin concentrations, adiponectin concentrations, HOMA-β-cell function, HOMA-insulin resistance, and insulin sensitivity index).

We used mixed-effects models to account for the correlation of repeated measurements within participants. Time dependence was allowed to vary across the subgroups, and quadratic and cubic terms for time were included in the three subgroups when significant (two-sided 5% significance level). For individuals who did not develop diabetes, year 0 was merely a timepoint in a normal life course, and thus we fitted the trajectories by linear models. We adjusted all analyses for age, sex, ethnic origin, and study phase. Pairwise differences in growth curves between the three subgroups were tested with the *F* test by comparing the curve of contrasts by diabetes subgroups with a straight line with zero slope that passes through the origin (two-sided 5% significance level). Accordingly, provided p values relate to curve differences in slope or intercept, or both. We did statistical analyses in R (version 9.15.0) and SAS (version 9.2).

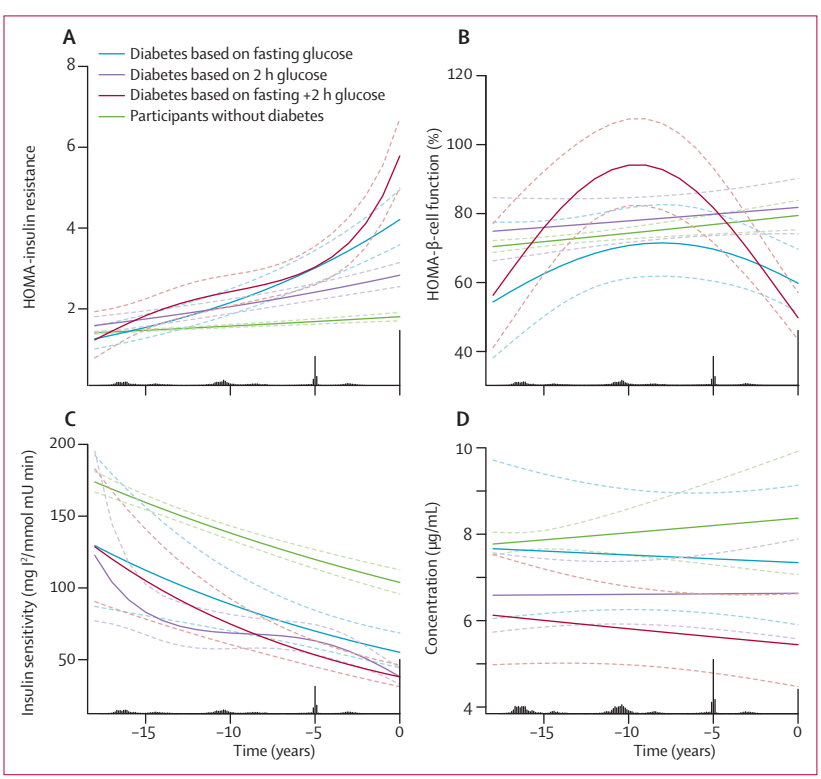

***Figure 2*: Trajectories of HOMA-insulin resistance (A), HOMA-β-cell function (B), insulin sensitivity index (C), and serum adiponectin concentrations (D) for a hypothetical, white, 60-year-old man (in year 0) from 18 years before diagnosis of type 2 diabetes or last clinical examination**

Time 0=diagnosis or last clinical examination. Solid lines are estimated trajectories and dashed lines are 95% CIs. Black bars show data distribution during follow-up. Adiponectin concentrations are based on a subset of data. HOMA=homoeostasis model of assessment.

To acknowledge that OGTTs are rarely done in clinical practice, we developed a classification tree for identification of individuals with type 2 diabetes who are likely to have the fasting and 2 h phenotype but for whom 2 h glucose concentrations are not available. We derived a classification tree for type 2 diabetes by both criteria based on a two-step approach—an initial screening of the explanatory variables listed in the table (not including 2 h glucose and drugs) by random forests analysis with fasting and 2 h concentrations as the outcome, and derivation of a classification tree based on the five highest ranking variables (appendix).

Role of the funding source

The sponsors of the study did not have roles in study design; data collection, analysis, and interpretation; or writing of the report. All authors accept full responsibility for the study, had full access to all the data, and take responsibility for the integrity of the data and the accuracy of the analysis. The corresponding author had the final responsibility to submit for publication.

Results

The Table shows characteristics of participants at the date of diagnosis for the three subgroups of type 2 diabetes or the last clinical examination for those without type 2 diabetes. Of the 274 people who developed type 2 diabetes, 55 (20·1%) had high fasting glucose concentrations, 148 (54·0%) had high 2 h concentrations, and 71 (25·9%) had high fasting and 2 h concentrations. At diagnosis (year 0), individuals with 2 h hyperglycaemia were older and had lower fasting insulin concentrations, HOMA-insulin resistance, and insulin sensitivity (as measured by the insulin senstivity index), but higher 2 h insulin concentrations and β-cell function than did those with fasting hyperglycaemia. Individuals with high fasting and 2 h glucose concentrations were generally more obese, had lower HDL cholesterol concentrations and β-cell function, and higher triglyceride and glycated haemoglobin A_{1c} (HbA_{1c}) concentrations and blood pressure than did the subgroups with high fasting concentrations or high 2 h concentrations only. Furthermore, the proportion of individuals with moderate or high cardiovascular risk was higher in the fasting and 2 h subgroup than in the fasting subgroup (table; p=0·02). For most variables, less than 5% of data were missing. However, for insulin resistance, β-cell function, insulin sensitivity index, waist–hip ratio, cardiovascular risk, and HDL and LDL cholesterol concentrations, 5–10% of data were missing.

Trajectories of fasting and 2 h glucose differed between the subgroups in accordance with the criteria by which type 2 diabetes was diagnosed (figure 1A, 1B; p<0·0001 for all comparisons). However, the curves did not diverge until roughly 6 years before diagnosis, when both fasting and 2 h glucose concentrations rose steeply in the fasting and 2 h subgroup. Fasting insulin concentrations rose slightly but steadily in the three diabetes subgroups from

15 years before diagnosis compared with those in participants without type 2 diabetes (figure 1C); this increase was less pronounced in the 2 h subgroup (p=0·037 compared with fasting subgroup and 0·0001 compared with fasting and 2 h subgroup). Heterogeneity between the subgroups was greater for the trajectories for 2 h insulin concentrations (figure 1D, p=0·0033 for fasting subgroup *vs* 2 h subgroup, 0·0326 for fasting subgroup *vs* fasting and 2 h subgroup, and <0·0001 for 2 h subgroup *vs* fasting and 2 h subgroup). In the fasting and 2 h subgroup, 2 h insulin concentrations peaked around 5 years before diagnosis and then started to fall, whereas 2 h insulin concentrations increased linearly in patients who developed type 2 diabetes according to fasting criteria or 2 h criteria, but at different rates (figure 1D; p=0·003 for fasting subgroup *vs* 2 h subgroup).

Trajectories of insulin resistance broadly resembled those of fasting glucose concentrations and differed significantly between all three subgroups (figure 2A; p<0·0001 for fasting subgroup *vs* 2 h subgroup and for 2 h subgroup *vs* fasting and 2 h subgroup, 0·0002 for fasting subgroup *vs* fasting and 2 h subgroup). Trajectories of β-cell function also differed significantly between the three subgroups (figure 2B; p=0·0002 for fasting subgroup *vs* 2 h subgroup, 0·0140 for fasting subgroup *vs* fasting and 2 h subgroup, and <0·0001 for 2 h subgroup *vs* fasting and 2 h subgroup). In the fasting and 2 h subgroup, percentage β-cell function increased until roughly 8–10 years before diagnosis and fell progressively thereafter (figure 2B). By contrast, patients in the 2 h subgroup had moderately stable values throughout follow-up (figure 2B). Individuals in the fasting subgroup had significantly lower HOMA-β-cell function from 18 years before diagnosis until diagnosis than did those who did not have type 2 diabetes (p<0·0001). Scores on the insulin sensitivity index were lower in the three subgroups of type 2 diabetes before and at diagnosis than they were in the participants who did not develop type 2 diabetes (p<0·0001 for all comparisons); scores decreased slightly faster in the 2 h subgroup and fasting and 2 h subgroup than in the fasting subgroup (figure 2C, p=0·0006 for fasting subgroup *vs* 2 h subgroup, and 0·0093 for fasting subgroup *vs* fasting and 2 h subgroup).

Individuals diagnosed by fasting and 2 h concentrations had lower serum adiponectin concentrations before diagnosis than did those diagnosed by either fasting or 2 h concentrations (figure 2D, p=0·0203 for fasting subgroup *vs* fasting and 2 h subgroup and 0·0504 for 2 h subgroup *vs* fasting and 2 h subgroup).

Body-mass indices and waist–hip ratios increased linearly with time in the three subgroups (figure 3A, 3B). However, obesity was more common in patients diagnosed by fasting and 2 h glucose concentrations than in those diagnosed by either fasting or 2 h concentrations (figure 3A, B; p=0·0029 for fasting subgroup *vs* fasting and 2 h subgroup and <0·0001 for 2 h subgroup *vs* fasting and 2 h subgroup).

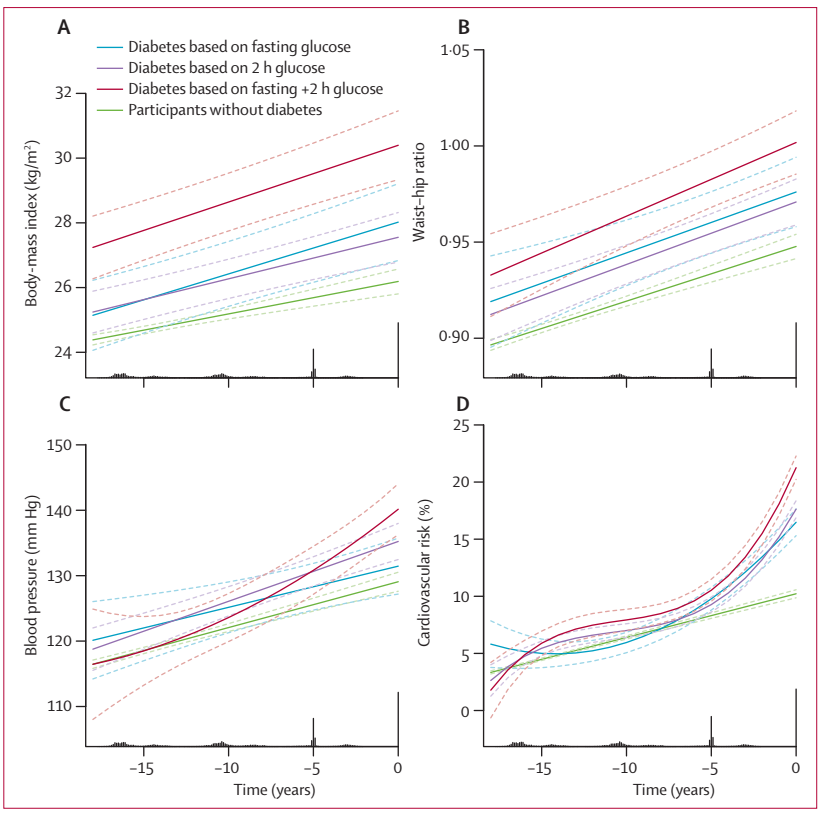

***Figure 3*: Trajectories of body-mass index (A), waist–hip ratio (B), systolic blood pressure (C), and 10 year absolute risk of cardiovascular disease (Framingham) (D) for a hypothetical, white, 60-year-old man (in year 0) from 18 years before diagnosis of type 2 diabetes or last clinical examination**

Time 0=diagnosis or last clinical examination. Solid lines are estimated trajectories and dashed lines are 95% CIs. Black bars show data distribution during follow-up.

The increase in both diastolic (data not shown) and systolic blood pressure with time was steepest in the subgroup diagnosed on the basis of fasting and 2 h glucose concentrations (figure 3C; p=0·0009 for fasting subgroup *vs* fasting and 2 h subgroup and 0·0150 for 2 h subgroup *vs* fasting and 2 h subgroup). Trajectories of estimated risk of cardiovascular disease differed significantly between the three subgroups (figure 3D; p=0·0024 for fasting subgroup *vs* 2 h subgroup and <0·0001 for fasting subgroup *vs* fasting and 2 h subgroup and 2 h subgroup *vs* fasting and 2 h subgroup); risk was highest in the fasting and 2 h subgroup (p<0·0001).

The trajectories of total and LDL cholesterol concentrations did not differ significantly between subgroups (figure 4A, 4B; p≥0·334 for all pairwise comparisons). However, HDL cholesterol concentrations decreased significantly more in the subgroup diagnosed on the basis of fasting and 2 h glucose concentrations than in that diagnosed on the basis of 2 h concentrations (figure 4C; p=0·0005), and patients diagnosed on the basis of both criteria had higher increases in concentrations of plasma triglycerides than did those diagnosed by either fasting or 2 h concentrations (figure 4D, p=0·0056 for fasting subgroup *vs* fasting and

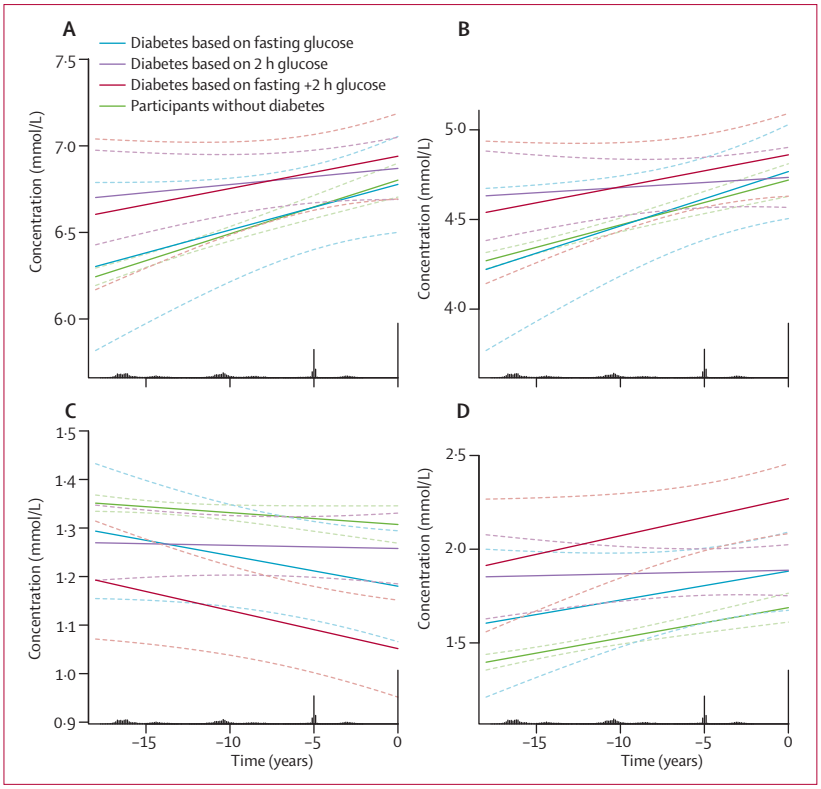

***Figure 4*: Trajectories for total cholesterol (A), LDL cholesterol (B), HDL cholesterol (C), and triglyceride (D) concentrations for a hypothetical, white, 60-year-old man (in year 0) from 18 years before diagnosis of type 2 diabetes or last clinical examination**

Time 0=diagnosis or last clinical examination. Solid lines are estimated trajectories and dashed lines are 95% CIs. Black bars show data distribution during follow-up.

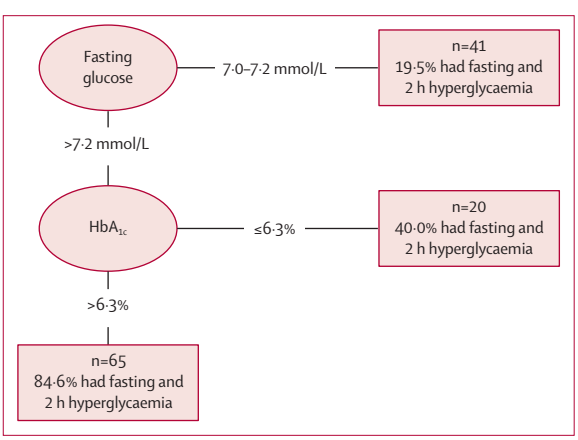

***Figure 5*: Classification tree for identification of patients with fasting and 2 h hyperglycaemia without results from an oral glucose tolerance test**

Sensitivity=78% (95% CI 68–87); specificity=82% (71–91); positive predictive value=85% (appendix). HbA_{1c}=glycated haemoglobin A_{1c}.

2 h subgroup and 0·0004 for 2 h subgroup *vs* fasting and 2 h subgroup).

In our study, 71 of the 126 (56·3%) individuals with fasting glucose concentrations in the diabetic range also had 2 h concentrations in the diabetic range; the 126 patients were used to derive the classification tree. The random forest analysis showed that the five highest ranking explanatory variables that discriminate between people diagnosed on the basis of fasting glucose concentrations only and those diagnosed on the basis of fasting and 2 h concentrations were fasting plasma glucose concentrations, HbA_{1c} concentrations, diastolic blood pressure, systolic blood pressure, and HOMA-insulin resistance. The resulting classification tree was based on these variables, but only fasting glucose and HbA_{1c} concentrations were significant in the model. 55 of 65 (85%) individuals with fasting plasma glucose concentrations greater than 7·2 mmol/L and HbA_{1c} greater than 6·3% (45 mmol/mol) had the fasting and 2 h phenotype (figure 5, appendix).

Discussion

We hypothesised that type 2 diabetes is not a single disease entity, but rather a heterogeneous disease with different underlying mechanisms preceding diagnosis in different groups of individuals. We did a simple stratification based on the common diagnostic glucose criteria of the Whitehall II cohort and showed that underlying pathogenesis differed as much as 18 years before diagnosis between patients with type 2 diabetes diagnosed on the basis of increased fasting glucose concentrations, those diagnosed on the basis of 2 h concentrations, and those diagnosed on the basis of both criteria (panel).

In the fasting and 2 h subgroup, HbA_{1c} concentrations surpassed the diagnostic threshold for type 2 diabetes (6·5%) at time of diagnosis, whereas, in the fasting subgroup and the 2 h subgroup, mean HbA_{1c} was less than the cutoff (6·0%) for high-risk type 2 diabetes.[14] Despite moderately normal HbA_{1c} concentrations, both the fasting subgroup and the 2 h subgroup had significantly increased estimated 10 year risk of cardiovascular disease compared with people without type 2 diabetes, suggesting that HbA_{1c} might not be a good marker of cardiovascular risk in all patients with type 2 diabetes.

Over the past two decades, the results of several studies[2,15,16] have suggested that fasting and post-OGTT hyperglycaemia represent phenotypes with distinct natural histories, a notion supported by our findings. We noted a long-standing reduction in basal β-cell function and a progressive increase in insulin resistance in patients developing type 2 diabetes diagnosed on the basis of fasting glucose concentrations. Thus, the increased fasting insulin concentration before onset (figure 1C) shows inadequate compensation for the increased insulin resistance.[17] Because of the low β-cell function in this subgroup before and at diagnosis, individuals with fasting hyperglycaemia might benefit from early prevention strategies focusing on prevention of further loss of β-cell function rather than strategies targeting peripheral insulin sensitivity. This line of thinking is supported by observational and interventional

studies[18,19] showing that physical activity, which mainly improves peripheral insulin sensitivity, has little effect on progression to type 2 diabetes in individuals with isolated impaired fasting glucose concentrations (ie, 2 h concentrations are normal), but is protective in those with impaired glucose tolerance (who have prediabetic 2 h glucose concentrations). By contrast, metformin, which mainly works by improving hepatic insulin sensitivity, seemed to be more effective in people with high fasting glucose concentrations than in those with low fasting concentrations in the Diabetes Prevention Program.[20]

To further disentangle the underlying causes of differences in patterns of insulin resistance and β-cell function between subgroups of type 2 diabetes, a detailed examination of the contributing genetic and non-genetic factors is needed. The effects of genes associated with 2 h glucose concentrations increase with age, whereas those of genes associated with fasting glucose concentrations are more stable with time,[21] suggesting different genetic effects in the different disease subgroups of our study.

In patients who developed type 2 diabetes diagnosed on the basis of 2 h concentrations, 2 h insulin concentrations increased exponentially, whole-body insulin sensitivity fell, and fasting β-cell function was stable and almost normal. However, the increase in insulin secretion 2 h after the OGTT was not sufficient to maintain 2 h plasma glucose concentrations within the non-diabetic range, suggesting peripheral insulin resistance with insufficient β-cell compensation.[17,22,23] In general, type 2 diabetes diagnosed on the basis of 2 h glucose concentrations accounts for 30–50% of all cases.[24] However, in clinical practice OGTTs are seldom done and thus illness often remains undiagnosed and untreated in individuals with the 2 h phenotype. Because 2 h glucose concentrations are more closely related to cardiovascular risk than are fasting glucose concentrations,[25,26] we expected that progression of blood pressure, concentrations of plasma lipids and adiponectin, and cardiovascular risk would be worse in patients in the 2 h subgroup than in those in the fasting subgroup. However, although the 2 h subgroup had a slightly higher estimated cardiovascular risk at time of diagnosis than did the fasting subgroup, they had a slower worsening of plasma lipids. A previous study[27] showed that a rapid rise in triglyceride concentrations precedes type 2 diabetes diagnosed on the basis of fasting glucose concentrations, but we did not confirm this finding. Rather, patients with increased fasting and 2 h glucose concentrations had higher triglyceride and lower adiponectin concentrations than did those in the other subgroups, independent of lipid-lowering treatment (data not shown).

The pattern of insulin secretion in the fasting and 2 h subgroup (increased β-cell function 10–15 years before diagnosis and subsequent decline thereafter) was not noted in the fasting subgroup or the 2 h subgroup, showing that the common notion that early β-cell compensation followed by a progressive loss of β-cell function is typical of the development of type 2 diabetes[1,28] seems only to apply to the fasting and 2 h subgroup, constituting roughly 25% of all screen-detected patients. This finding also supports the idea that increases of both fasting and 2 h glucose concentrations are not merely a mixture of the underlying conditions of isolated fasting or 2 h hyperglycaemia, but rather a distinct disease entity.[3]

To identify patients with progressively declining β-cell function, accelerated increase of glucose concentrations, and high cardiovascular risk, knowledge of the patients' subtype can be useful. Because OGTTs are not done on a regular basis in primary care, other methods to identify individuals in the high-risk subgroup might be needed. We noted that 85% of individuals with a fasting glucose concentration greater than 7·2 mmol/L and HbA_{1c} concentration greater than 6·3% (45 mmol/mol) also had 2 h glucose concentrations in the diabetic range. Thus, the combination of fasting glucose and HbA_{1c} concentrations might be useful to identify high-risk individuals who have accelerated β-cell dysfunction and are especially likely to benefit from early glucose-lowering treatment and intensified cardiovascular disease prevention. However, this finding needs to be confirmed in independent datasets.

***Panel:* Research in context**

Systematic review

We searched PubMed for studies of adults (≥19 years) published in English before Dec 18, 2012, with the terms "type 2 diabetes" and "heterogeneity" in the title or abstract. Of the 157 references returned, 72 were focused on genetics of type 2 diabetes. The remaining 85 publications included 34 reviews or meta-analyses, eight clinical trials, and 43 observational studies. 35 publications concerned the pathogenesis of type 2 diabetes. We searched the reference lists in these publications and selected citations that we judged relevant. We noted no previous studies investigating metabolic features preceding development of subtypes of type 2 diabetes diagnosed by fasting versus 2 h glucose concentrations.

Interpretation

Individuals with prediabetes differ in their natural history and underlying pathogenesis dependent on whether they have increased fasting glucose concentrations or increased 2 h glucose concentrations, or both. We showed that such differences are also present in individuals with incident type 2 diabetes. To distinguish between patients with isolated fasting hyperglycaemia and those with fasting and 2 h hyperglycaemia is important, because these subgroups have distinct natural histories of β-cell dysfunction and cardiovascular risk. More research is needed to understand how the specific mechanisms that trigger type 2 diabetes can be used to optimise treatment and prevention of complications.

Our study has some limitations. Estimates of insulin sensitivity and β-cell function were based on HOMA and the insulin sensitivity index, which are calculated from fasting and 2 h glucose and insulin concentrations and thus might overlap the classification of the three subgroups of type 2 diabetes at diagnosis. However, individuals in the fasting subgroup had very different trajectories of HOMA-β-cell function than did those in the fasting and 2 h subgroup, despite diagnoses based on fasting glucose concentrations in both. Whitehall II was an occupational cohort, which might not be representative for a general European population. Nonetheless, no evidence suggests that the trajectories in our study would not apply to other populations, although the distribution of the different subgroups of disease might vary between populations. For example, Asian populations have a higher prevalence of diabetes based on fasting glucose concentrations and they develop type 2 diabetes at lower body-mass indices than do white populations.[24,29,30]

For the **Whitehall II data sharing policy** see http://www.ucl.ac.uk/whitehallII/data_sharing/index.htm

We were not able to describe sex-specific trajectories because of the low proportion of women in the study. Such findings would have been highly relevant because men have higher fasting glucose concentrations than do women.[31] Furthermore, with the acceptance of HbA_{1c} for use in diagnosis, trajectories of HbA_{1c} concentrations in the different subgroups would have been relevant, but concentrations were measured only in the last two clinical phases. Another limitation is that we had to exclude a substantial proportion of incident cases diagnosed outside the Whitehall II study because of unknown or missing OGTT results, which could limit the generalisability of our findings. However, that participants with doctor-diagnosed diabetes would represent a different disease group from those diagnosed on the basis of an OGTT seems unlikely. All trajectories for doctor-diagnosed patients were within the range of the three diabetes subgroups, supporting this suggestion (data not shown).

In conclusion, type 2 diabetes seems to have different natural history and pathogenesis dependent on whether it is diagnosed on the basis of increased fasting glucose concentrations or increased 2 h glucose concentrations, or both. Future studies should establish whether glycaemic control, drug needs, and the incidence of cardiovascular disease and microvascular complications differ between patients with different subgroups of disease. Additionally, a better understanding of the genetic and non-genetic causative factors associated with different subgroups is needed. Ultimately, assessment of the need for stratified prevention and treatment strategies is important.

Contributors

KF conceived the idea and wrote the first draft, with major input from DV. DV planned and did the statistical analysis. All authors critically assessed and reviewed the paper. MK obtained funding for the Whitehall II study.

Conflicts of interest

Steno Diabetes Center, where KF and DV are employed, receives part of its core funding from unrestricted grants from the Novo Nordisk Foundation and Novo Nordisk, and is owned by Novo Nordisk. KF, DV, and DRW own shares in Novo Nordisk. All other authors declare that they have no conflicts of interest.

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