Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study

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Summary

Background Little is known about the timing of changes in glucose metabolism before occurrence of type 2 diabetes. We aimed to characterise trajectories of fasting and postload glucose, insulin sensitivity, and insulin secretion in individuals who develop type 2 diabetes.

Methods We analysed data from our prospective occupational cohort study (Whitehall II study) of 6538 (71% male and 91% white) British civil servants without diabetes mellitus at baseline. During a median follow-up period of 9·7 years, 505 diabetes cases were diagnosed (49·1% on the basis of oral glucose tolerance test). We assessed retrospective trajectories of fasting and 2-h postload glucose, homoeostasis model assessment (HOMA) insulin sensitivity, and HOMA β-cell function from up to 13 years before diabetes diagnosis (diabetic group) or at the end of follow-up (non-diabetics).

Findings Multilevel models adjusted for age, sex, and ethnic origin confirmed that all metabolic measures followed linear trends in the group of non-diabetics (10 989 measurements), except for insulin secretion that did not change during follow-up. In the diabetic group (801 measurements), a linear increase in fasting glucose was followed by a steep quadratic increase (from 5·79 mmol/L to 7·40 mmol/L) starting 3 years before diagnosis of diabetes. 2-h postload glucose showed a rapid increase starting 3 years before diagnosis (from 7·60 mmol/L to 11·90 mmol/L), and HOMA insulin sensitivity decreased steeply during the 5 years before diagnosis (to 86·7%). HOMA β-cell function increased between years 4 and 3 before diagnosis (from 85·0% to 92·6%) and then decreased until diagnosis (to 62·4%).

Interpretation In this study, we show changes in glucose concentrations, insulin sensitivity, and insulin secretion as much as 3–6 years before diagnosis of diabetes. The description of biomarker trajectories leading to diabetes diagnosis could contribute to more-accurate risk prediction models that use repeated measures available for patients through regular check-ups.

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Introduction

The current global focus on prevention of type 2 diabetes points out the need to understand better the pathophysiological changes leading to diabetes at the earliest possible stage.[1–5] Although prediabetic conditions—such as impaired fasting glycaemia or impaired glucose tolerance—can predict the risk of developing diabetes, these only indicate an individual's glycaemic state at a single point in time.[6–9] The risk of developing diabetes and macrovascular complications might already be present at glucose concentrations below the current cut-off for prediabetes.[10,11]

The multistage model of diabetes development describes an unstable period before diabetes onset.[12] Although this model is widely accepted and supported by several studies,[13–25] important questions remain unanswered. An abrupt increase in fasting glucose might happen 1·5–3 years before diagnosis, but the exact trend of this increase is unknown.[14,19,22] Only one study in Pima Indians[21] described postload glucose trajectories before diabetes diagnosis on the basis of annual measurements, whereas other studies on changes in postload glucose are based on measurements repeated at least 3 years apart.[14] Prospective studies[13,15–18,20,23–25] have measured or estimated insulin sensitivity and insulin secretion with sophisticated methods, but generally describe changes as a function of the stage preceding diabetes rather than of time.

Because data from previous studies provide a poorly defined picture of diabetes development, we aimed to assess the multistage model of diabetes development in a large population. To improve timing of screening and prevention, high-resolution data that describe the timing of early changes in glucose metabolism before occurrence of type 2 diabetes should be obtained. In this study from the longitudinal Whitehall II cohort of British civil servants, we characterised population trajectories of fasting glucose, 2-h postload glucose, insulin sensitivity,

and insulin secretion during 13 years of follow-up, and compared such trajectories between those who did and did not develop type 2 diabetes.

Methods

Participants and study design

All 35–55-year-old non-industrial British civil servants working in London offices (UK) of 20 departments were invited to participate in this study. 10 308 (6895 men) were recruited between August, 1985, and April, 1988 (phase 1).[26] Between August, 1991, and December, 1994 (phase 3), all participants known to be alive and in the country were invited to the screening clinic for an oral glucose tolerance test, and 6058 men and 2758 women (85·5% of the original sample) attended. Screening was repeated between April, 1997, and August, 1999 (phase 5; 5444 men and 2385 women), and between October, 2002, and September, 2004 (phase 7; 4894 men and 2074 women). Additional questionnaire-only phases assessed diabetes status between January, 1995, and July, 1996 (phase 4; 5928 men and 2700 women), between January and December 2001 (phase 6; 5151 men and 2204 women), and between February, 2006, and June, 2007 (phase 8; 5017 men and 2156 women). The University College London ethics committee reviewed and approved the study, and written informed consent was obtained from each participant.

For more on **HOMA2 calculator** see http://www.dtu.ox.ac.uk/index.php?maindoc=/homa/index.php

For the analysis, when oral glucose tolerance test was done for the first time, phase 3 served as the baseline. After the exclusion of non-participants (n=1492) and individuals with prevalent diabetes at phase 3 (n=42), those with missing follow-up (n=552), missing ethnic-origin data (n=27), or serum values not suitable for homoeostasis model assessment (HOMA) analysis at any screening visit (n=1657), the final sample consisted of 6538 participants (74% of the baseline sample). Participants included in the analyses were more likely to be white (91% *vs* 89%, p=0·001) and men (71% *vs* 63%, p<0·0001) than those excluded. They were also 1·8 years younger (95% CI 1·5 to 2·1), had 0·12 mmol/L higher fasting glucose (0·06 to 0·18), and 8 pmol/L higher fasting insulin (4 to 11) than excluded participants. Body-mass index did not differ (–0·16, –0·37 to 0·05 kg/m²) between the groups.

Of the potential 19 614 person-examinations that would have been generated if every participant completed all three screenings, 398 related to screenings after diabetes diagnosis and were excluded. We also excluded 5188 person-examinations because they were not fasting according to WHO criteria (<8 h fasting or afternoon sampling); 108 because fasting plasma glucose values were extreme (≤3 or ≥25 mmol/L); and 2130 because fasting insulin values were extreme (≤20 or ≥400 pmol/L), exceeding the published validity ranges for HOMA calculations.[27,28] Thus, the dataset for analysis included a total of 11 790 person-examinations.

Measurements

During all phases of the study, we handled samples according to similar standard protocols. We took venous blood samples in individuals who were fasting (≥8 h of fasting) before undergoing a standard 2-h oral glucose tolerance test. Glucose samples were drawn into fluoride monovette tubes and insulin samples into native tubes, which were centrifuged on site within 1 h. Plasma or serum was immediately removed from the monovette tubes, and moved into microtubes and stored at –70°C. We measured blood glucose with the glucose oxidase method[29] on YSI model 23A glucose analyser (phase 3, mean coefficient of variation [CV] 2·9–3·3%)[30] and YSI model 2300 STAT PLUS analyser (phases 5 and 7, mean CV 1·4–3·1%)[31] (YSI Corporation, Yellow Springs, OH, USA), and serum insulin with an in-house human insulin radioimmunoassay (phase 3, mean CV 7%)[32] and a DAKO insulin ELISA kit (DakoCytomation Ltd, Ely, UK) (phases 5 and 7, mean CV 4·2–9·3%).[33] We calculated HOMA insulin sensitivity and HOMA β-cell function on the basis of model-derived estimates (rather than linear approximations) with the HOMA2 calculator version 2.2.[27,28]

Diabetes was defined by a fasting glucose of 7·0 mmol/L or more, or a 2-h postload glucose of 11·1 mmol/L or more.[34,35] During the duration of follow-up (median 9·7 years; interquartile range [IQR] 7·9–14·2), we diagnosed 505 diabetes cases mostly on the basis of 75 g oral glucose tolerance test (248 cases, 49%), except for those reporting doctor-diagnosed diabetes (179 cases, 35%), or use of diabetes medication (78 cases, 15%) at screening or additional questionnaire phases.

Statistical analysis

Statistical analyses were undertaken using SPSS version 14.0 statistical software. We divided participants into two groups: those who developed and those who did not develop diabetes during the follow-up period. The observation period started at the date of diagnosis (year 0) for those who became diabetic, and at the last screening or questionnaire phase for non-diabetics. Participants were then traced backwards to their first clinical screening. Data at each phase during this retrospective observation period were collated to build trajectories for each outcome (fasting glucose, 2-h glucose, HOMA insulin sensitivity, and HOMA β-cell function). For example, a participant who reported diagnosed diabetes at phase 8 has his time 0 at the midpoint of phases 7 and 8 (estimated time of diagnosis), and has three measurements: one at phase 7, about 1 year before the event; another at phase 5, about 6 years before the event; and another at phase 3, about 11 years before the event. As shown in figures 1 and 2, measurements were well distributed throughout the 13-year time window of the study because of the variation in screening dates and dates of diabetes diagnosis.

	Incident diabetes (N=505)	Non-diabetics (N=6033)	p value
Age (years)	53·1 (6·6)	52·6 (7·1)	0·12
Male	66%	71%	0·029
White	80%	92%	<0·0001
Body-mass index (kg/m²)	28·18 (4·99)	25·60 (3·63)	<0·0001
Fasting glucose (mmol/L)	5·71 (0·91)	5·21 (0·47)	<0·0001
2-h postload glucose (mmol/L)	7·06 (2·48)	5·38 (1·42)	<0·0001
Fasting insulin (pmol/L)	73 (30)	47 (30)	<0·0001
2-h postload insulin (pmol/L)	473 (351)	259 (222)	<0·0001
HOMA2-%S	103·4 (58·8%)	145·1% (63·2%)	<0·0001
HOMA2-%B	88·5 (39·0%)	78·4% (30·3%)	<0·0001

Data are mean (SD) or percentage. Comparisons were done with two-sample *t* tests or Fisher's exact tests, as appropriate. HOMA2-%S and HOMA2-%B were calculated using HOMA2 calculator version 2.2 (Diabetes Trials Unit, University of Oxford, Oxford, UK).[27,28] HOMA2-%S=homoeostasis model assessment insulin sensitivity. HOMA2-%B=homoeostasis model assessment β-cell function.

Table 1: **Baseline characteristics of incident diabetes cases and non-diabetics**

In a preliminary analysis, we plotted these trajectories as a function of time, and fitted non-parametric curves with locally weighted scatterplot smoother for graphical representation. We then used multilevel longitudinal modelling to estimate trajectories of fasting glucose, 2-h glucose, HOMA insulin sensitivity, and HOMA β-cell function in diabetics before diagnosis and in non-diabetics before last screening.[36] Data were organised so that repeated measurements of the three screening phases (ie, person-examinations) were nested within participants and the non-independence of the person-examinations (the same individuals contributed more than one person-examination in the dataset) was taken into account in estimating standard errors. We modelled differences in trajectories between diabetics and non-diabetics with either a linear or non-linear growth model.

We treated observation time as one period (a non-piecewise approach) or two distinct periods (a piecewise approach).[37] In the latter approach, we created two time variables: a continuous variable centered at the start of the second period (time=0) and a dummy variable indicating the period (0=1st period and 1=2nd period). We first established the most parsimonious model for each centring point (from –9 to 0) and then chose the centering point that had the lowest information criteria for the final model.

All analyses were adjusted for age, sex, ethnic origin, and study phase. To provide figures adjusted for baseline characteristics, trajectories were fitted for a hypothetical population of 71% male, 91% white individuals 63 years old at the end of follow-up. Finally, we checked how the models matched the non-parametric scatterplot curves from the preliminary analysis (webappendix p 5) and ran some sensitivity analyses to test whether our findings were robust (webappendix pp 2–4). Statistical significance was inferred at a two-tailed p<0·05.

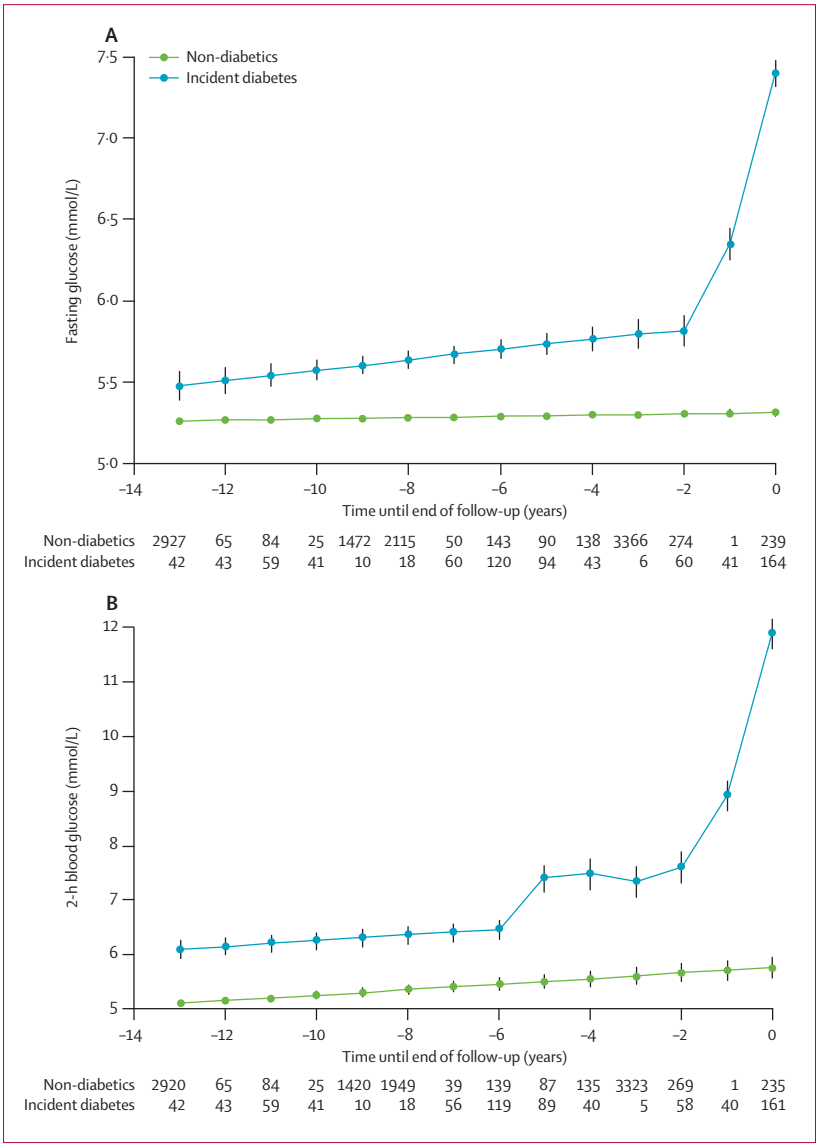

Figure 1: **Fasting (A) and 2-h postload (B) glucose trajectories before diagnosis of diabetes or the end of follow-up**

Numbers are 505 incident diabetes cases and 6033 non-diabetics. Time 0 is diagnosis for incident diabetes cases or end of follow-up for non-diabetics. Multilevel longitudinal modelling was done using linear growth model for non-diabetic and piecewise approach, including cubic terms for time, for incident diabetic individuals with oral glucose tolerance test fasting glucose (A) and 2-h glucose (B) as outcomes. Analysis was adjusted for age, sex, ethnic origin, and study phase. Estimations were done for a hypothetical population consisting of 71% male, 91% white individuals aged 63 years at time 0 years. Error bars show 95% CI for the fixed effects. Tables show the number of measurements for each year at and before diabetes diagnosis or the end of follow-up.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

See **Online** for webappendix

	Fasting glucose (mmol/L)	2-h postload glucose (mmol/L)	HOMA2-%S	HOMA2-%B
Time (per year)	0·004† (0·001)	0·051† (0·007)	–1·11%‡ (0·30)	..
Case	0·50† (0·04)	0·99† (0·09)	–34·21%† (3·15)	10·45%† (1·55)
Case×time	0·028‡ (0·007)	..	..	..
Case×time×2nd period	–0·27¶ (0·09)	1·54† (0·22)	–2·76%¶ (0·85)	12·13%‡ (3·21)
Case×time^2×2nd period	0·26† (0·027)	–0·75† (0·10)	..	–4·44%† (0·84)
Case×time^3×2nd period	..	0·11† (0·01)	..	..

Data are regression coefficient (SE). Time=a continuous variable centred (time=0) at 3 years before diagnosis or the end of follow-up for fasting glucose, 6 years for postload glucose, 5 years for HOMA2-%S, and 4 years for HOMA2-%B. 2nd period=a dummy variable: 1 for positive values in the time variable and 0 for non-positive values. Case=incident diabetes case. HOMA2-%S=homoeostasis model assessment insulin sensitivity. HOMA2-%B=homoeostasis model assessment β-cell function. *Trajectories in 505 incident diabetes cases were compared with those in 6033 non-diabetics. Multilevel longitudinal modelling used a linear growth model for non-diabetic and a piecewise approach, including cubic terms for time, for incident diabetic individuals with oral glucose tolerance test fasting glucose, 2-h glucose, HOMA2-%S, and HOMA2-%B as outcomes. Data were adjusted for age, sex, ethnic origin, and study phase. Only models with the lowest information criteria are shown for each outcome. †p<0·0001. ‡p<0·001. ¶p<0·01.

Table 2: **Fixed effects for multilevel models of change for fasting glucose, 2-h postload glucose, HOMA insulin sensitivity, and HOMA β-cell function before diagnosis of diabetes or the end of follow-up***

Results

The 505 incident diabetic participants contributed a total of 801 fasting measurements, and the 6033 non-diabetics contributed 10 989. The mean age did not differ between groups (table 1). As expected, incident diabetic cases were less likely to be men and white, and had higher body-mass index than non-diabetics (table 1). At baseline, they also had higher fasting and postload plasma glucose, fasting and postload insulin, and HOMA β-cell function, and a lower HOMA insulin sensitivity (all p<0·0001).

Non-diabetics had a slight increase of fasting plasma glucose over time (mean [SE] 0·004 mmol/L [0·001] per year), with fasting plasma glucose concentrations of 5·26 mmol/L (0·008) 13 years before diagnosis and 5·31 mmol/L (0·010) at the end of follow-up (figure 1A and table 2). For incident diabetes cases, we saw a linear trend of fasting plasma glucose from 13 years to 3 years before diagnosis but with a steeper slope than non-diabetics (slope difference 0·028 mmol/L [0·007] per year). Fasting plasma glucose values were 5·47 mmol/L [0·04] 13 years before diagnosis and 5·79 mmol/L [0·04] at 3 years before diagnosis (figure 1A). In the last 3 years before diagnosis, the trajectory followed a quadratic curve reaching 7·40 mmol/L (0·04) at the time of diagnosis.

In non-diabetics, 2-h postload glucose increased from 5·11 mmol/L (0·024) to 5·77 mmol/L (0·098) during the 13 years of assessment, with a slope of 0·051 mmol/L (0·007) per year (figure 1B and table 2). The slopes were not significantly different between the diabetes and the non-diabetes groups from 13 to 6 years before the end of follow-up, but diabetes cases had a 0·99 mmol/L (0·09) higher glucose value throughout this period.

From the 6 years before diagnosis to the end of follow-up, postload glucose concentrations of incident diabetes cases followed a cubic trajectory with a flat part from 5 to 3 years before diagnosis. The difference of postload glucose concentrations was about 1·5 times larger between incident cases and non-diabetics during this period than in the preceding period from 13 to 6 years before diagnosis (figure 1B). Diabetes cases had a rapid increase of glucose concentrations from 2 years before diagnosis onward (from 7·60 mmol/L [0·15] to 11·90 mmol/L [0·13]).

From 13 to 5 years before the end of follow-up, HOMA insulin sensitivity decreased linearly with the same slope of 1·11% (0·30) per year in diabetes cases and non-diabetics (figure 2A and table 2). Those with incident diabetes had a 34·2% (3·1) lower insulin sensitivity during this period. In the 5 years before diagnosis, HOMA insulin sensitivity decreased with a steeper slope in diabetes cases than in non-diabetics (difference in slopes per year 2·76% [0·85]), reaching 86·7% (4·7) at the end of follow-up (figure 2A).

The calculated insulin secretion (HOMA β-cell function) did not change for either participant group between 13 and 4 years before the end of follow-up (figure 2B and table 2). However, HOMA β-cell function of 85·0% (1·5) in diabetes cases was, on average, 10·4% (1·5) higher than that in non-diabetics. During the 4 years before diagnosis, HOMA β-cell function values of diabetes cases followed a negative quadratic trajectory with a steep increase to 92·6% (2·5) between years 4 and 3 before diagnosis, followed by a steep decrease to 62·4% (2·3) between 3 years before diagnosis and end of follow-up (figure 2A).

The models for trajectories of fasting and postload glucose, HOMA insulin sensitivity, and HOMA β-cell function (table 2) were supported in several sensitivity analyses: in an extended study population, including also those with 5–8 h of fasting (n=7148, sensitivity analysis 1); in a subgroup of participants with no missing data before diagnosis (diabetics) or phase 8 (non-diabetics) (n=1332, sensitivity analysis 2); and when the timing of diabetes was set to the midpoint between date of diagnosis and the preceding examination to calculate the onset of disease (n=6290, sensitivity analysis 3) (webappendix p 2). Adjustment for time-varying body-mass index attenuated the difference in insulin sensitivity between diabetics and non-diabetics, but it had little effect on the differences in trajectories between groups (webappendix p 4).

Discussion

We describe the 13-year trajectories of fasting and postload blood glucose, insulin sensitivity, and insulin secretion until diabetes diagnosis in a large middle-aged, metabolically healthy population at baseline. All changes in metabolic measures in individuals who did not develop diabetes were well described by linear trajectories (modest rises for fasting and postload glucose, steady values for insulin secretion, and slight falls for insulin sensitivity). In individuals who developed diabetes, the levels of fasting and postload glucose and insulin secretion were higher, and insulin sensitivity was lower, than those in controls as

early as 13 years before diagnosis. In incident diabetes cases, linear increases in fasting and postload glucose were followed by a rapid increase in levels 6 to 3 years before diagnosis. HOMA insulin sensitivity showed a steep decrease during the last 5 years before diagnosis and HOMA β-cell function increased between years 4 and 3 before diagnosis, and then decreased until diagnosis.

Our findings support a multistage model of diabetes aetiology:[12] a long compensatory period, when insulin secretion increases to compensate insulin resistance without any major changes in glucose values; a stable adaptation, when β-cell mass is decreasing in spite of β-cell adaptation; and a transient unstable period with a rapid rise of glucose to overt diabetes. Our results suggest a stable adaptation when fasting blood glucose values increase linearly with a steeper slope in people who later develop diabetes than in healthy participants, whereas postload glucose increases in a similar way to that of controls. The observed accelerated rises fit with the unstable period leading to diabetes.

Our study is in agreement with several other studies[14,19,22] that showed an abrupt increase in fasting glucose values 1·5 to 3 years before diagnosis of diabetes. We observed an increase of 0·02–0·8 mmol/L in glucose per year across the whole 13-year observation period before diabetes diagnosis; this is in agreement with annual increases in glucose reported previously (range 0·4–1·2 mmol/L),[14,19,22] and confirmed previous observations about rapid increases in fasting glucose in impaired glucose tolerance or when β-cell dysfunction is present.[25,38] However, none of these studies did a continuous prediction of fasting glucose similar to our study, and most of them were based on fewer cases (<200) and a shorter follow-up period.

Our findings on postload glucose trajectories are similar to those in smaller-scale studies. A study including three data collections showed 5–6 mmol/L increase of postload glucose in the 7 years preceding diabetes.[14] In younger Pima Indians (mean age at diagnosis 46 years), a linear increase of postload glucose up to 4–8 years before diabetes diagnosis with a similar slope was also found.[21] Our results confirm findings of the abrupt increase of postload glucose and extend it to a broader, mostly white, population.[21]

Low insulin sensitivity seems to be a prerequisite for incident diabetes.[13,16–18,20,24,25] Scarce evidence exists on the association between insulin sensitivity and development of impaired glucose tolerance.[16,17,20,24] The decrease in insulin sensitivity in those who develop impaired glucose tolerance does not differ from that observed in people who remain normoglycaemic, but is much smaller than in those who develop incident diabetes.[16] This is in agreement with our findings that show that the decreased insulin sensitivity before the 4 years preceding diabetes diagnosis was similar to that in normoglycaemic controls, but a steeper decrease in insulin sensitivity was seen during the few years immediately before diagnosis.

The role of insulin secretion and β-cell function as predictors of type 2 diabetes is unclear. Most studies report no association between insulin secretion and diabetes,[13,16,19,24,39] whereas the association of low disposition index with diabetes is well established.[13,16,17,20,24] Furthermore, evidence exists of a higher insulin secretion in impaired glucose tolerance than in normal glucose tolerance, and a lower insulin secretion in diabetes than in impaired glucose tolerance, at least in non-Asian populations.[15,23]

Our findings suggest that part of the explanation for inconsistencies in the above described results might arise from differences in time frames between studies. High values of insulin secretion might be associated with increased risk of type 2 diabetes if measured years or

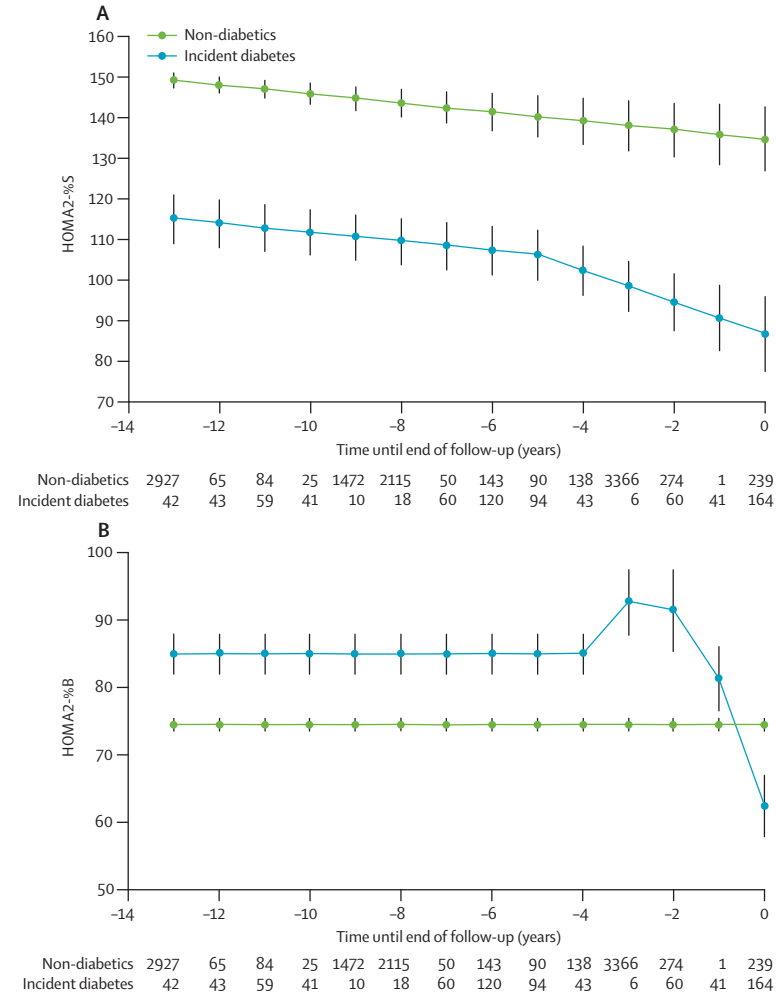

Figure 2: **Homoeostasis model assessment (HOMA) insulin sensitivity (A) and HOMA β-cell function trajectories (B) before diagnosis of diabetes or the end of follow-up**
Numbers are 505 incident diabetes cases and 6033 non-diabetics. Time 0 is diagnosis for incident diabetes cases or end of follow-up for non-diabetics. Multilevel longitudinal modelling was done using linear growth model for non-diabetic and non-piecewise or piecewise approach, including linear or quadratic terms for time, for incident diabetic individuals with HOMA2-%S (A) and HOMA2-%B (B) as outcomes. Analysis was adjusted for age, sex, ethnic origin, and study phase. Estimations were done for a hypothetical population consisting of 71% male, 91% white individuals aged 63 years at time 0 years. Error bars show 95% CI for the fixed effects. Tables show the number of measurements for each year at and before diabetes diagnosis or the end of follow-up. HOMA2-%S=homoeostasis model assessment insulin sensitivity. HOMA2-%B=homoeostasis model assessment β-cell function.

decades before diagnosis, but low values predict the short-term diabetes risk. This is consistent with longitudinal studies reporting modest changes in acute insulin response or even in disposition index during the transition from normal to impaired glucose tolerance, but substantial decreases during further progression to diabetes.[16,17,24] Further research is needed to assess whether timing of the changes in insulin secretion, insulin sensitivity, and fasting and postload glucose points to causal relations between these indexes.

Our study benefits from a well phenotyped and well described occupational cohort of people and diagnosis of incident diabetes based on oral glucose tolerance test using the current definition of the disease.[26,34] We applied a sophisticated approach for data analysis taking into account the inter-relation between repeated measurements from the same individual at different timepoints. The long follow-up time provided a unique opportunity to describe different periods of prediabetes status according to trajectories based on piecewise modelling.

The inclusion of the diagnostic glucose value in the analysis might be criticised because any diagnostic threshold would produce a rapid rise in the mean in those who exceed this threshold.[21] To overcome this issue, we refitted the multilevel models excluding the diagnostic value from the analysis. These models produced similar trajectories to those presented here. Furthermore, several other reports[14,19,21,22] suggest a rapid rise in fasting and 2-h glucose values, and the modelling of individual growth curves of postload glucose also supports the presence of a rapid rise at the time of diagnosis.[21] These findings suggest that we might have detected a genuine prediagnosis trajectory in glucose values.

We used measures of HOMA insulin sensitivity and insulin resistance, which are well accepted in the published literature. HOMA insulin sensitivity is extensively validated against the gold standard clamp and minimal model methods.[28,40] However, the calculated insulin secretion is less widely used.[28,40,41] Because HOMA uses fasting values for estimation, it mostly describes hepatic insulin resistance and steady-state insulin secretion. Although hepatic insulin resistance is strongly correlated with muscle and fat insulin resistance, the steady-state insulin secretion is a late marker of β-cell dysfunction and shows only a moderate correlation with the most sensitive measures of the first-phase insulin secretion.[28,42] Therefore, our findings might be an underestimation of the timing of early β-cell decompensation.

We did not use disposition index to describe changes in glucose metabolism with a single parameter because its calculation based on HOMA values has several theoretical issues and the compensation described by it could be incomplete even in normal glucose-tolerant individuals.[42–44]

Data from almost 20 000 blood glucose values provide an excellent power to assess general trajectories in a piecewise model based on between-subject and within-subject comparisons. The proposed trajectories give a good description of the events leading to diabetes. However, the restricted number of repeated observations for each participant (maximum three) means that individual differences in trajectories could not be identified in these data and should be studied in the future.

Of the baseline population, 26% was excluded because of missing data, extreme glucose or insulin values, or prevalent diabetes. Selection bias is an unlikely explanation for our results because comparisons of participants included and excluded from analyses revealed modest differences, although statistical significance was often reached because of large numbers. In the main analysis, we excluded individuals who had fasted less than 8 h, but sensitivity analyses showed that inclusion of those who had fasted 5–8 h (the Whitehall II protocol) had little effect on the findings. Furthermore, the main findings were replicated in a subgroup with no missing data, suggesting that missing data are an unlikely source of bias in this study.

The description of biomarker trajectories leading to diabetes diagnosis could contribute to future attempts of building more-accurate risk prediction models that use the wealth of repeated measures available for patients through regular check-ups. These models might give an indication of which trajectory best describes an individual's results. We anticipate that these models will have a better prediction than those that use only the most recent glucose measurements.

Our findings show various opportunities for screening and prevention. Although most prevention studies focused on prediabetic people, our findings suggest that people with prediabetes are already on the steep part of the glucose trajectory. We hypothesise that prevention would be more effective before this unstable period, but more research is needed to identify people at this stage of disease development. If a person could be kept on the linear part of the fasting glucose (or postload glucose[21]) trajectory, the onset of diabetes might be substantially delayed. Further research is needed to confirm or refute these hypotheses.

Contributors

AGT contributed to the study concept and design, acquisition of data, analysis and interpretation of data, drafting and critical revision of the manuscript, statistical analysis, and study supervision. MJ and TNA contributed to analysis and interpretation of data, critical revision of the manuscript, and statistical analysis. EJB contributed to analysis and interpretation of data, critical revision of the manuscript, and funding. MK contributed to study concept and design, analysis and interpretation of data, drafting and critical revision of the manuscript, funding, and study supervision. DRW contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting and critical revision of the manuscript, funding, and study supervision.

Conflicts of interest

We declare that we have no conflicts of interest.

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