# Supplemental Material

## SCIENTIFIC MEMBERS OF THE CONSORTIUM

See Table S1.

## DATA

### Examinations

Examinations were performed in the morning after a 10-hour overnight fast. Participants remained on their usual non-antidiabetic medications; metformin, if used, was stopped for the 24 hours preceding the study visit and restarted immediately after. Anthropometric data, blood pressure, and urine samples were collected. An intravenous cannula was inserted into a forearm vein according to local protocols. Baseline blood samples were immediately collected for analysis of glutamic acid decarboxylase and islet antigen-2 antibodies, glucagon-like peptide-1, glucagon, insulin, C-peptide, $HbA_{1c}$, and DNA.

### Mixed-meal tolerance test (MMTT)

Before the MMTT, fasting samples for glucose, insulin and C-peptide analysis were collected. The MMTT consisted of a 250 ml Fortisip liquid drink (18.4 g carbohydrate per 100 ml) over a period of 2–5 min. Blood samples were collected every 30 min for two hours for subsequent glucose, insulin and C-peptide assays.

### Biochemistry assays

Measurements were performed by a central laboratory. Plasma glucose was measured by the enzymatic colorimetric assay GOD-PAP, using Roche MODULAR P analyzers (Hoffmann-La Roche, Basel, Switzerland). Plasma insulin and C-peptide were measured by electrochemiluminescence, using Roche E170 analyzers (Hoffmann-La Roche). $HbA_{1c}$ was measured by ion-exchange high-performance liquid chromatography, using Tosoh G8 analyzers (Tosoh Bioscience, San Francisco, CA, USA).

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured by UV absorbance without pyridoxal phosphate activation. Gamma-glutamyl transferase (GGT) was measured by enzymatic colorimetric assay. Serum creatinine and albumin were measured with the Creatinine Jaffé method and the bromocresol green method, respectively. Cholesterol was measured by enzymatic colorimetric methods, HDL-cholesterol was measured directly using PEG-modified enzymes and dextran sulphate, triacylglycerol was measured by quantitative determination with glycerol blanking. AST, ALT, GGT, serum creatinine and albumin, cholesterol, HDL-cholesterol and triacylglycerol were measured using a Roche MODULAR P analyzer (Roche Diagnostics, Indianapolis, IN, USA). LDL-cholesterol was calculated from the Friedewald formula.

Intact proinsulin was measured using the TECO Medical Intact Proinsulin ELISA kit in use on the Dynex DS2 analyzer. Glucagon, glutamic acid decarboxylase (GAD) and islet antigen-2 antibodies (IA-2) were measured using a DS2 Elisa robot, Dynex technologies.

Plasma samples for glucagon-like peptide-1 (GLP-1) measurement were collected in P800 tubes (Becton Dickinson, Wokingham, UK) to prevent intrinsic proteolysis. Intact GLP-1 was measured using MSD GLP-1 active kit (product code K150JWC; Meso Scale Diagnostics, Rockville, MD, USA). Total GLP-1 was assayed using MSD GLP-1 total kit (product code K150JVC; Meso Scale Diagnostics).

Each biochemical assay was performed using validated standard methods. Reference samples were included in all procedures to control for inter-assay variation, and the laboratory regularly participated in international external quality assessment schemes.

### Body composition

Body mass index (BMI) was calculated as weight divided by height squared, and waist circumference was measured at the level of the umbilicus at mid-respiration. The hepatic steatosis index (HSI) was calculated as described previously (1).

### Abdominal MRI

The volume of adipose tissue was measured using MRI, as described elsewhere (2). Total abdominal adipose tissue was separated into intra-abdominal adipose tissue, also referred to as “visceral” fat, and abdominal subcutaneous adipose tissue. Liver and pancreas fat and iron were derived simultaneously using a multiecho MRI technique (2–4).

### Dietary data

Self-reported dietary intake was assessed by 24-hour multi-pass method, using food habit and 24-hour recall questionnaires. Nutritional analysis was undertaken using Dietplan-7 software (Forestfield Software Ltd, Horsham,

UK). All diet coders were trained by a lead research dietician/nutritionist using a study specific operational manual protocol. Detailed description of the coding and diet analysis protocol are reported elsewhere (5).
Dietary patterns were assessed in concordance with the WHO dietary guidelines using the validated "Healthy Diet Indicator" (HDI) (6); a higher HDI score indicates a more favorable diet. The score was calculated from the dietary intakes of all food and drink consumed except alcohol, which was analyzed separately.

**Physical activity intensity and sedentary behaviour**
Participants were fitted with a wrist-worn triaxial accelerometer (ActiGraph GT3X+; Actigraph LLC, Pensacola, FL, USA) for measurement of physical activity, sedentary behavior and sleep over 10 days. The monitor was fitted to the participant's non-dominant wrist using an adjustable strap. The participant was requested to wear the monitor continuously for 10 days to allow habitual uninterrupted measures of both sleep and physical activity. The monitor was set to record at 30 Hz with the manufacturer's sleep mode disabled. High-pass-filtered vector magnitude (hpfVM) was derived as described elsewhere (7). In this analysis, we used the 10-day mean hpfVM and the percentage of hpfVM values $\leq$ 48 m*g* as measures of physical activity intensity and sedentary behavior.

**Type 2 diabetes (T2D) polygenic risk score**
A T2D polygenic risk score was computed from the 403 single-nucleotide polymorphisms (SNPs) and the respective effect sizes reported for T2D in Mahajan et al. (8). The individual score values were obtained by summing up the number of risk alleles at each locus multiplied by its effect size.

**Additional questionnaires**
Questionnaire data were collected on alcohol consumption, smoke habits, family history of diabetes and medication history.

The whole set of traits considered in this study is reported in Table S2.

## METHODS

**Area under the curves and mean values**
Areas under the curve (AUC) of several MMTT variables were computed according to the trapezoidal rule and mean values as AUC/time interval.

**Mathematical modelling of β-cell function**
From MMTT glucose and C-peptide, the following β-cell function parameters were calculated by mathematical modelling (9): glucose sensitivity (GS), i.e., the slope of the relationship between glucose concentration and insulin secretion rate; rate sensitivity (RS), marker of early insulin release; insulin secretion rate at 8 mmol/l glucose (ISRstd); potentiation factor ratio (PR), the ratio between the potentiation factor at 2- and 0-hours, ; total insulin secretion (ISRtot), i.e., the AUC of insulin secretion during the whole MMTT. Insulin secretion rate was calculated from C-peptide using Van Cauter's C-peptide model (10).

**Insulin clearance**
Fasting insulin clearance (CLIb) was calculated as the ratio between fasting insulin secretion and fasting insulin concentration. The MMTT insulin clearance (CLIm) was calculated as the ratio of the AUCs of insulin secretion and insulin concentration during the MMTT.

**Mathematical modelling of $HbA_{1c}$ progression rate**
The HbA1c trajectories were described with a conditional linear mixed-effect model (11). The conditional approach employs a linear transformation of the data to derive a longitudinal and a cross-sectional component, which are orthogonal. The transformation makes modelling of the longitudinal component independent of the cross-sectional effects: the former is relevant for quantification of $HbA_{1c}$ progression rate, while the latter are potential confounders that need not to be considered in the conditional approach. In particular, the approach eliminates possible spurious correlations between the longitudinal parameters and baseline $HbA_{1c}$, which may arise if baseline $HbA_{1c}$ is not accurately modelled.
The longitudinal $HbA_{1c}$ component was described as the sum of the following terms:

- a proportional effect of time, described by the parameter $r_i$, where *i* represents a specific individual, represented as a random variable with a normal distribution;
- a proportional effect of BMI;
- a linear effect of the metformin dose, expressed as percentage of a maximal dose of 3 grams;

- a linear effect of the cumulative dose for the other antidiabetic drugs (insulin excluded), expressed as sum of the percentages of the maximum dose of each drug;
- a constant effect of insulin treatment;
- a proportional effect of delay in $HbA_{1c}$ assay, i.e. of the difference between the time of measurement and the time of sample collection;
- a residual error $\varepsilon_{ik}$, where $k$ refers to the time point, represented as a random variable from a normal distribution with zero mean.

The insulin and BMI effects were constrained to be negative and positive, respectively. The linear effects of the treatment *dose* were modelled as 0 for *dose*=0, and as $a+b \cdot dose$ for *dose*>0, where $a$ and $b$ were different for metformin and the other antidiabetic drugs and were constrained to be negative. Maximum doses for antidiabetic drugs different from metformin and insulin were fixed to the values in Table S3. A medication was considered effective at a given time if it was taken at least 30 days before.
The $r_i$ parameter represents the $HbA_{1c}$ underlying progression rate, adjusted for changes in BMI and antidiabetic treatments.
The model parameters were estimated using Monolix 2016 R1(12), which implements the SAEM algorithm for estimation of mixed-effect models. In a first step, the software identifies mean and standard deviation of the population distribution of the model parameters with inter-individual variability (in our case just $r$). In the second step, the software computes the individual estimates of the parameters (in our case $r_i$) by simultaneously fitting the data and using the previously estimated distributions as priors (*maximum a posteriori* estimation).
The parameter estimates of the $HbA_{1c}$ progression model are reported in Table S4. The BMI and treatment effects were concordant with what shown in the literature(13), considering the low baseline $HbA_{1c}$ values in this study (6.41±0.53 %, 46.5±5.8 mmol/mol, mean ± standard deviation).

**Progression rates for other traits**
The progression rates for all other traits were derived in the same way as for $HbA_{1c}$, but without including the effect of treatments and assay delay. The BMI effect was included only in the models for OGIS and QUICKI. The BMI effects on OGIS and QUICKI progression rates were -8.68±11% (estimate±relative standard error) ml $min^{-1}$ $kg^{-1}$ and -0.00157±9% $m^2$ $kg^{-1}$, respectively.

**On the multivariable analyses**
Baseline values of the β-cell function parameters of some subjects were discarded due to high uncertainty in their estimates.

## RESULTS

**Progression rates of $HbA_{1c}$ and other traits**
$HbA_{1c}$ was measured at two visits in 6% of participants, at three visits in 15% of participants, at four visits in 75% of participants, and at five visits in 4% of participants.
In 50% of the subjects, T2D was managed via lifestyle only along the whole study.
The estimates of the progression rates for $HbA_{1c}$, adjusted for changes in BMI and in diabetes medications, and for the other traits are reported in Figure S1 (histogram for $HbA_{1c}$ progression rates only) and Table S5.

**Variables associated with $HbA_{1c}$ progression rate**
The pairwise associations between $HbA_{1c}$ progression rate and baseline values and progression rates of the investigated traits are shown in Figure S2.
The standardized coefficients and the $p$ values of the independent variables included in the multivariable linear analysis of $HbA_{1c}$ progression rate are shown in Table S6. The table presents different regression models, all adjusted for sex, baseline age and center, and considering different subsets of subjects, based on the availability of different subsets of variables. The models described include those with a unique independent variable (models named "-1"), a model with the adjustment variables only (model "0"), and models including or excluding the effects of baseline liver fat or visceral fat, and the effects of baseline BMI and fasting HDL-cholesterol, found to have non-significant effects once visceral or liver fat is included in the analysis. The models presented in the main text are numbered "1" and "9".
In the multivariable linear analysis, the indices of insulin sensitivity OGIS and QUICKI, as well as HOMA-IR (14), Stumvoll (15) and Matsuda (16) indices (data not shown), were interchangeable in terms of overall analysis results, with OGIS producing the best performance (adjusted $R^2$ 0.38 *vs* 0.33, 0.37, 0.28 and 0.29, respectively; $N$ = 625).

**Variables associated with fast *vs* average $HbA_{1c}$ progression**
The logistic analysis reported in the main text defines fast *vs* average progressors based on a threshold on $HbA_{1c}$ progression rate that clearly separate the two groups (0.255 %/year, 2.79 mmol $mol^{-1}$ $year^{-1}$, Figure S1). We found that

this threshold corresponds to $(q_{50} - q_1) + q_{50}$, where $q_1$ and $q_{50}$ are the 1st and 50th quantiles of the distribution of individual $HbA_{1c}$ progression rates. The use of lower thresholds allows the identification of larger sets of fast progressors. In particular, using the 2nd, 5th or 10th quantile instead of the 1st quantile in the formula, thresholds of 0.200, 0.143 or 0.121 %/year (2.19, 1.56 or 1.32 mmol $mol^{-1}$ $year^{-1}$), respectively, are obtained, with a corresponding number of fast progressors of *N*=61, *N*=110 or *N*=131 subjects, respectively, instead of *N*=33 (Figure S1).
With the lower thresholds, discrimination capacity, sensitivity, specificity and accuracy of the logistic model described in the main text remain very similar (Figure S3). The effects of the independent variables of the logistic model are also essentially unaffected (Figure S3). In all cases, it appears that stronger deterioration and a lower baseline value of OGIS and GS, and CLIm increase are independently associated with fast progression. Minor differences are the following: the effect of HDL reduction is significant with all thresholds apart from 0.200 %/year; the effect of baseline HDL is significant only using thresholds 0.143 and 0.121 %/year; the effect of baseline CLIm is significant only with the lowest threshold (0.121 %/year); the effect of baseline $HbA_{1c}$ is significant with all lower thresholds but not with the original one.
The percentage of patients without diabetes medications along the whole study was higher in average than in fast progressors (51% *vs* 30%, *p*=0.021 from two-sided Chi-square test with α=0.05). At baseline, the percentages of fast progressors and of average progressors treated with metformin were not different: 39.4% [24.7-56.3%, 95% CI] *vs* 33.9% [30.5-37.5%], respectively (*p* = 0.64). At the last visit, the percentage of fast progressors treated with any diabetes medication, 66.7% [49.6-80.2%], was somewhat higher than the percentage of average progressors treated with any diabetes medication, 47.5% [43.8-51.2%] (*p* = 0.048). This difference was driven by a larger use of diabetes medications other than metformin or insulin in fast progressors (30.3% [17.4-47.3%] *vs* 5.0% [3.6-6.9%], *p* = 3E-8). Again at the last visit, the number of patients treated with insulin (seven average progressors) was too low to derive any trustworthy comparison between percentages of fast and average progressors treated with insulin (0.0% [0.0-10.4%] and 1.0% [0.5-2.1%], respectively, *p* = 0.74).

## REFERENCES


1. Lee J-H, Kim D, Kim HJ, Lee C-H, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2010 Jul;42(7):503–8.

2. Thomas EL, Fitzpatrick JA, Malik SJ, Taylor-Robinson SD, Bell JD. Whole body fat: content and distribution. Prog Nucl Magn Reson Spectrosc. 2013 Aug;73:56–80.

3. O'Regan DP, Callaghan MF, Wylezinska-Arridge M, Fitzpatrick J, Naoumova RP, Hajnal JV, et al. Liver fat content and T2*: simultaneous measurement by using breath-hold multiecho MR imaging at 3.0 T--feasibility. Radiology. 2008 May;247(2):550–7.

4. St Pierre TG, Clark PR, Chua-Anusorn W. Measurement and mapping of liver iron concentrations using magnetic resonance imaging. Ann N Y Acad Sci. 2005;1054:379–85.

5. Gibson R, Eriksen R, Lamb K, McMeel Y, Vergnaud A-C, Spear J, et al. Dietary assessment of British police force employees: a description of diet record coding procedures and cross-sectional evaluation of dietary energy intake reporting (The Airwave Health Monitoring Study). BMJ Open. 2017 Apr 1;7(4):e012927.

6. Jankovic N, Geelen A, Streppel MT, de Groot LCPGM, Orfanos P, van den Hooven EH, et al. Adherence to a Healthy Diet According to the World Health Organization Guidelines and All-Cause Mortality in Elderly Adults From Europe and the United States. Am J Epidemiol. 2014 Nov 15;180(10):978–88.

7. Brage S, Westgate K, Wijndaele K, Godinho J, Griffin S, Wareham N. Evaluation of a method for minimising diurnal information bias in objective sensor data. In: Int Conf Amb Mon Phys Act Mov. 2013.

8. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat Genet. 2018 Nov;50(11):1505–13.

9. Mari A, Tura A, Gastaldelli A, Ferrannini E. Assessing Insulin Secretion by Modeling in Multiple-Meal Tests: Role of Potentiation. Diabetes. 2002 Feb 1;51(Supplement 1):S221–6.

10. Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of Insulin Secretion Rates from C-Peptide Levels. Comparison of Individual and Standard Kinetic Parameters for C-Peptide Clearance. Diabetes. 1992 Jan 3;41(3):368–77.

11. Verbeke G. Conditional Linear Mixed Models. Am Stat. 2001;55(1):25–34.

12. Lixoft. MONOLIX [Internet]. 2016. Available from: http://lixoft.com/products/monolix/

13. DeFronzo RA, Stonehouse AH, Han J, Wintle ME. Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. Diabet Med J Br Diabet Assoc. 2010 Mar;27(3):309–17.

14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985 Jul;28(7):412–9.

15. Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Järvinen H, Van Haeften T, et al. Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. Diabetes Care. 2000 Mar;23(3):295–301.

16. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care. 1999 Sep;22(9):1462–70.

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**Table S2. Subjects' baseline traits.**

| Trait | Abbreviation | Baseline value* | *N* |
|---|---|---|---|
| **Age (years)** | age | 62±8 | 732 |
| **Sex (males)** | - | 58 | 732 |
| **Body mass index (kg/m$^2$)** | BMI | 30.4±4.9 | 732 |
| **Waist circumference (cm)** | waist | 103±13 | 727 |
| **Systolic blood pressure (mm Hg)** | BPsys | 131±16 | 621 |
| **Diastolic blood pressure (mm Hg)** | BPdia | 75±10 | 621 |
| **Type 2 diabetes family history** | - | 39 | 682 |
| **On metformin**$^\dagger$ | - | 34 | 732 |
| **Metformin dosage for subjects on metformin (g)**$^\dagger$ | - | 1.0±0.5 | 732 |
| **$HbA_{1c}$ (%, mmol/mol)** | $HbA_{1c}$ | 6.41±0.53, 46.5±5.8 | 728 |
| **Fasting glucose (mmol/l)**$^\dagger$ | gb | 7.1±1.4 | 731 |
| **Fasting insulin (pmol/l)**$^\dagger$ | ib | 106±69 | 730 |
| **Mean MMTT glucose (mmol/l)**$^\dagger$ | gm | 9.3±2.1 | 730 |
| **Mean MMTT insulin (pmol/l)**$^\dagger$ | im | 459±279 | 730 |
| **Fasting insulin secretion (pmol min$^{-1}$ m$^{-2}$)**$^\dagger$ | ISRb | 136±48 | 730 |
| **Total MMTT insulin secretion (nmol/m$^2$)**$^\dagger$ | ISRtot | 44±15 | 730 |
| **Fasting triacylglycerol (mmol/l)** | TG | 1.51±0.78 | 732 |
| **Fasting total cholesterol (mmol/l)** | CHO | 4.22±1.15 | 732 |
| **Fasting LDL-cholesterol (mmol/l)** | LDL | 2.34±0.95 | 727 |
| **Fasting HDL-cholesterol (mmol/l)** | HDL | 1.18±0.39 | 732 |
| **Aspartate aminotransferase (U/l)** | AST | 25.6±11.1 | 732 |
| **Alanine aminotransferase (U/l)** | ALT | 26.2±13.8 | 732 |
| **AST/ALT ratio (unitless)** | AST/ALT | 1.09±0.48 | 732 |
| **Gamma-glutamyl transferase (U/l)** | GGT | 51±71 | 732 |
| **Serum creatinine (µmol/l)** | SCr | 74.7±17.9 | 732 |
| **Serum albumin (g/l)** | ALB | 39.7±2.6 | 165 |
| **Fasting intact glucagon-like peptide-1 (pg/ml)** | iGLP1 | 0.64±0.91 | 725 |
| **Fasting total glucagon-like peptide-1 (pg/ml)** | tGLP1 | 9.5±9.3 | 724 |
| **1-h total glucagon-like peptide-1 (pg/ml)** | tGLP1.60 | 19±16 | 722 |
| **Fasting glucagon (pg/ml)** | GLG | 111±52 | 704 |
| **1-h glucagon (pg/ml)** | GLG.60 | 107±39 | 717 |
| **2-h glucagon (pg/ml)** | GLG.120 | 103±25 | 184 |
| **1-h GLP-1 increment (pg/ml)** | GLP1inc.60 | 9.8±12.7 | 718 |
| **1-h glucagon increment (pg/ml)** | GLGinc.60 | -3±52 | 693 |
| **2-h glucagon increment (pg/ml)** | GLGinc.120 | -6±33 | 183 |
| **1-h intact proinsulin (pmol/l)** | proins.60 | 22±14 | 359 |
| **1-h intact proinsulin to insulin ratio (unitless)** | proins/ins.60 | 0.05±0.04 | 358 |
| **Insulin sensitivity (ml min$^{-1}$ m$^{-2}$)** | OGIS | 300±74 | 728 |
| **Fasting insulin sensitivity (unitless)** | QUICKI | 0.136±0.014 | 730 |
| **β-cell glucose sensitivity (pmol min$^{-1}$ m$^{-2}$ mmol$^{-1}$ l)** | GS | 85±56 | 714 |
| **β-cell rate sensitivity (pmol m$^{-2}$ mmol$^{-1}$ l)** | RS | 1138±1102 | 714 |
| **Insulin secretion rate at 8 mmol/l glucose (pmol min$^{-1}$ m$^{-2}$)** | ISRstd | 228±135 | 714 |
| **Potentiation factor ratio (unitless)** | PR | 1.4±0.6 | 713 |
| **Fasting insulin clearance (l min$^{-1}$ m$^{-2}$)** | CLIb | 1.60±1.02 | 730 |
| **MMTT insulin clearance (l min$^{-1}$ m$^{-2}$)** | CLIm | 0.93±0.30 | 730 |
| **Hepatic steatosis index (unitless)** | HSI | 41.5±5.9 | 730 |
| **Fatty liver index (unitless)** | FLI | 67±27 | 725 |
| **Type 2 diabetes polygenic risk score (unitless)** | PRS | 25.2±0.7 | 732 |
| **Liver fat (%)** | liver fat | 9±7 | 480 |

| Trait | Abbreviation | Baseline value* | *N* |
|---|---|---|---|
| **Liver iron content (mg/g tissue)** | liver iron | 1.6±0.5 | 486 |
| **Pancreas fat (%)** | pancreas fat | 12±8 | 488 |
| **Pancreas iron content (mg/g tissue)** | pancreas iron | 1.4±0.5 | 509 |
| **Intra-abdominal adipose tissue (l)** | visceral fat | 5.5±2.2 | 429 |
| **Abdominal subcutaneous adipose tissue (l)** | subcutaneous fat | 8.0±3.7 | 429 |
| **Physical activity intensity (m*g*)** | PA | 35±10 | 674 |
| **Sedentary behavior (% of time)** | SED | 83±4 | 674 |
| **Smoking habits (%, current, ex, never)** | - | 13, 50, 37 | 732 |
| **Average alcohol consumption (%, regularly, occasionally, never)** | - | 58, 25, 17 | 732 |
| **24-h energy intake (kcal)** | - | 1828±625 | 644 |
| **24-h protein intake (g)** | - | 89±35 | 644 |
| **24-h fat intake (g)** | - | 73±34 | 644 |
| **24-h saturated fat intake (g)** | - | 26±14 | 644 |
| **24-h added sugars intake (g)** | - | 65±40 | 644 |
| **24-h carbohydrate intake (g)** | - | 221±91 | 644 |
| **24-h energy intake-adjusted non-starch polysaccharides (g/kcal)** | - | 8.7±3.3 | 644 |
| **24-h energy intake-adjusted fruit & vegetables (g/kcal)** | - | 227±145 | 644 |
| **24-h energy intake-adjusted wholegrains (g/kcal)** | - | 26±22 | 644 |
| **24-h energy intake-adjusted fish (g/kcal)** | - | 20±39 | 644 |
| **24-h energy intake-adjusted red meat (g/kcal)** | - | 46±49 | 644 |
| **24-h percentage of total energy intake from protein (%)** | - | 20±6 | 644 |
| **24-h percentage of total energy intake from fat (%)** | - | 36±9 | 644 |
| **24-h percentage of total energy intake from saturated fat (%)** | - | 13±5 | 644 |
| **24-h percentage of total energy intake from added sugars (%)** | - | 19±8 | 644 |
| **24-h percentage of total energy intake from carbohydrate (%)** | - | 49±11 | 644 |
| **Healthy diet indicator** | HDI | 4.7±2.6 | 644 |
| **Healthy diet indicator quartiles (% in quartiles 1, 2, 3 and 4)** | - | 23, 25, 26, 26 | 644 |

* Data are mean ± standard deviation of the inter-individual distribution, or percentage.

† Trait not included in the stepwise multivariable analyses.

MMTT: mixed meal test.

**Table S3. Maximum doses for antidiabetic drugs different from insulin.**

| Drug | Max Dose (mg) | Weekly (W) or Daily (D) |
|---|---|---|
| Acarbose | 600 | D |
| **Metformin** | 3000 | D |
| Dapagliflozin | 10 | D |
| Empagliflozin | 25 | D |
| Alogliptin | 25 | D |
| Sitagliptin | 100 | D |
| Dulaglutide | 1.5 | W |
| Liraglutide | 1.8 | D |
| Gliclazide | 320 | D |
| Glimepiride | 4 | D |
| Glipizide | 20 | D |
| Tolbutamide | 2000 | D |

**Table S4. Parameter estimates of the $HbA_{1c}$ progression model.**

| Parameter | Estimate | RSE (%) |
|---|---|---|
| *r* (%/year, mmol $mol^{-1}$ $year^{-1}$) | 0.0627, 0.685* | 17 |
| BMI effect (% $kg^{-1}$ $m^{-2}$, mmol $mol^{-1}$ $kg^{-1}$ $m^{-2}$) | 0.131, 1.43 | 8 |
| Metformin effect: *a* (%, mmol/mol) | -0.0942, -1.03 | 74 |
| Metformin effect: *b* (%, mmol/mol) | -0.00145, -0.0159 | 101 |
| Metformin effect with 100% dose (%, mmol/mol) | -0.240, -2.62 | - |
| Other antidiabetic treatment effect: *a* (%, mmol/mol) | -0.0970, -1.06 | 153 |
| Other antidiabetic treatment effect: *b* (%, mmol/mol) | -0.00161, -0.0176 | 138 |
| Other antidiabetic treatment effect with 100% dose (%, mmol/mol) | -0.258, -2.82 | - |
| Insulin effect (%, mmol/mol) | -0.0970, -1.06 | 205 |
| Assay delay effect (%/day, mmol $mol^{-1}$ $day^{-1}$) | -0.00047, -0.00516 | 19 |

RSE: relative standard error of the estimate.

* Mean value of the population distribution.

**Table S5. Estimates of the progression rates of the investigated traits.**

| Trait | Abbreviation | Progression rate* | 95% CI | Relative progression rate† | *N* |
|---|---|---|---|---|---|
| **Body mass index (kg $m^{-2}$ $year^{-1}$)** | BMI | -0.0089±0.52 | -0.058,0.040 | -0.03 | 732 |
| **Waist circumference (cm $year^{-1}$)** | waist | 0.54±1.3 | 0.37,0.71 | 0.52 | 719 |
| **$HbA_{1c}$ (%/year, mmol $mol^{-1}$ $year^{-1}$)** | $HbA_{1c}$ | 0.063±0.18, 0.69±2.0 | 0.041,0.085, 0.45,0.93 | 0.98, 1.47 | 732 |
| **Total MMTT insulin secretion (nmol $m^{-2}$ $year^{-1}$)‡** | ISRtot | 0.44±2.4 | 0.13,0.75 | 1.00 | 653 |
| **Fasting triacylglycerol (mmol $l^{-1}$ $year^{-1}$)** | TG | 0.038±0.14 | 0.016,0.060 | 2.50 | 719 |
| **Fasting total cholesterol (mmol $l^{-1}$ $year^{-1}$)** | CHO | -0.012±0.22 | -0.039,0.015 | -0.28 | 719 |
| **Fasting LDL-cholesterol (mmol $l^{-1}$ $year^{-1}$)** | LDL | -0.046±0.18 | -0.070,-0.023 | -1.94 | 713 |
| **Fasting HDL-cholesterol (mmol $l^{-1}$ $year^{-1}$)** | HDL | 0.016±0.040 | 0.009,0.023 | 1.36 | 719 |
| **Aspartate aminotransferase (U $l^{-1}$ $year^{-1}$)** | AST | 1.2±3.6 | 0.77,1.63 | 4.77 | 719 |
| **Alanine aminotransferase (U $l^{-1}$ $year^{-1}$)** | ALT | 0.53±10 | -0.39,1.45 | 2.01 | 719 |
| **AST/ALT ratio ($year^{-1}$)** | AST/ALT | 0.039±0.04 | 0.024,0.054 | 3.61 | 719 |
| **Serum creatinine (µmol $l^{-1}$ $year^{-1}$)** | SCr | -0.21±1.2 | -0.58,0.16 | -0.29 | 719 |
| **Insulin sensitivity (ml $min^{-1}$ $m^{-2}$ $year^{-1}$)** | OGIS | -8.5±19 | -10.7,-6.3 | -2.82 | 649 |
| **Fasting insulin sensitivity ($year^{-1}$)** | QUICKI | -0.0013±0.0025 | -0.0016,-0.0010 | -0.95 | 653 |
| ***β*-cell glucose sensitivity (pmol $min^{-1}$ $m^{-2}$ $mmol^{-1}$ l $year^{-1}$)** | GS | -1.9±5.0 | -3.4,-0.4 | -2.19 | 653 |
| ***β*-cell rate sensitivity (pmol $m^{-2}$ $mmol^{-1}$ l $year^{-1}$)** | RS | -22±98 | -57,13 | -1.91 | 653 |
| **Insulin secretion rate at 8 mmol/l glucose (pmol $min^{-1}$ $m^{-2}$ $year^{-1}$)** | ISRstd | -5.2±19 | -8.5,-1.9 | -2.29 | 653 |
| **Potentiation factor ratio ($year^{-1}$)** | PR | -0.0035±0.11 | -0.023,0.016 | -0.25 | 652 |
| **Fasting insulin clearance (l $min^{-1}$ $m^{-2}$ $year^{-1}$)** | CLIb | -0.039±0.34 | -0.070,-0.008 | -2.46 | 653 |
| **MMTT insulin clearance (l $min^{-1}$ $m^{-2}$ $year^{-1}$)** | CLIm | -0.00069±0.046 | -0.0072,0.0058 | -0.07 | 653 |
| **Hepatic steatosis index ($year^{-1}$)** | HSI | -0.31±0.68 | -0.40,-0.22 | -0.74 | 717 |

* Data are mean ± standard deviation of the inter-individual distribution, and are expressed as units/year (e.g. %/year or mmol $mol^{-1}$ $year^{-1}$ for $HbA_{1c}$).

† Ratio between mean progression rate and mean baseline value (from Table S2), as percentage per year.

‡ Progression rate not included in the stepwise multivariable analyses.

CI: confidence interval on the estimate of the mean; MMTT: mixed meal test.

**Table S6. Standardized coefficients (with *p* values as superscripts) and adjusted $R^2$ from multivariable linear analysis of $HbA_{1c}$ progression rate.**

| Model | Sex | Age bas | OGIS progr | CLIm progr | GS progr | TG progr | HDL progr | RS progr | OGIS bas | CLIm bas | $HbA_{1c}$ bas | GS bas | BMI bas | HDL bas | Visceral fat bas | Liver fat bas | Adjusted $R^2$ | *N* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **-1** | - | - | -0.24*** | 0.16*** | -0.23*** | 0.25*** | -0.11** | $-0.07^{0.07}$ | -0.11** | -0.11** | $0.02^{0.58}$ | $-0.06^{0.13}$ | 0.15*** | -0.18*** | 0.27*** | 0.19*** | - | 625* |
| **0** | $-0.04^{0.61}$ | -0.15*** | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.04 | 625 |
| **1** | $0.12^{0.08}$ | $-0.03^{0.31}$ | -0.57*** | 0.28*** | -0.25*** | 0.15*** | -0.14*** | -0.09* | -0.52*** | 0.21*** | -0.20*** | -0.14*** | 0.10** | -0.10* | - | - | 0.38 | 625 |
| **2** | 0.21* | -0.08* | -0.61*** | -0.08* | -0.27*** | 0.30*** | -0.11* | 0.13** | -0.53*** | 0.22*** | -0.22*** | -0.15** | $0.09^{0.07}$ | $-0.05^{0.37}$ | - | - | 0.40 | 407 (liver fat bas available) |
| **3** | $0.15^{0.10}$ | $-0.06^{0.16}$ | -0.60*** | -0.12** | -0.28*** | 0.25*** | -0.14** | 0.17*** | -0.57*** | 0.22*** | -0.20*** | -0.17** | $0.06^{0.24}$ | $-0.11^{0.05}$ | - | - | 0.40 | 373 (visceral fat bas available) |
| **4** | 0.18* | $-0.08^{0.06}$ | -0.59*** | -0.08* | -0.28*** | 0.30*** | -0.11* | 0.13** | -0.49*** | 0.24*** | -0.24*** | -0.16** | $0.08^{0.10}$ | $-0.03^{0.51}$ | - | 0.10* | 0.40 | 407 |
| **5** | 0.25* | $-0.08^{0.06}$ | -0.58*** | -0.12** | -0.27*** | 0.24*** | -0.13** | 0.17*** | -0.55*** | 0.24*** | -0.21*** | -0.16** | $0.01^{0.87}$ | $-0.11^{0.06}$ | 0.14* | - | 0.41 | 373 |
| **6** | $0.14^{0.14}$ | $-0.08^{0.7}$ | -0.63*** | 0.25*** | -0.26*** | 0.17*** | -0.10* | -0.10* | -0.54*** | 0.21*** | -0.21*** | -0.16** | - | - | - | 0.12* | 0.40 | 320 (both visceral fat bas and liver fat bas available) |
| **7** | 0.26** | -0.11* | -0.63*** | 0.25*** | -0.25*** | 0.16*** | $-0.08^{0.10}$ | -0.11* | -0.56*** | 0.23*** | -0.20*** | -0.14* | - | - | 0.16** | - | 0.41 | 320 (both visceral fat bas and liver fat bas available) |
| **8** | 0.17* | -0.09* | -0.61*** | 0.30*** | -0.27*** | 0.13** | -0.10* | $-0.08^{0.06}$ | -0.50*** | 0.19*** | -0.23*** | -0.16** | - | - | - | 0.11* | 0.40 | 408 |
| **9** | 0.19* | -0.09* | -0.62*** | 0.24*** | -0.16** | 0.18*** | -0.10* | -0.12** | -0.56*** | 0.21*** | -0.20*** | -0.16** | - | - | 0.15** | - | 0.40 | 374 |

Model (-1): $HbA_{1c}$ progression rate = sex + age bas + center + variable (each column represents a specific model, and the various models are given in a unique row for sake of clarity).
Model (0): $HbA_{1c}$ progression rate = sex + age bas + center.
Model (1): $HbA_{1c}$ progression rate = sex + age bas + center + OGIS progr + CLIm progr + GS progr + TG progr + HDL progr + RS progr + OGIS bas + CLIm bas + $HbA_{1c}$ bas + GS bas + BMI bas + HDL bas. This is the model in Figure 1, panel A.
Model (2): Model (1), with different *N* (see last column).
Model (3): Model (1), with different *N* (see last column).
Model (4): Model (1) + liver fat bas.
Model (5): Model (1) + visceral fat bas.
Model (6): $HbA_{1c}$ progression rate = Sex + Age bas + center + OGIS progr + CLIm progr + GS progr + TG progr + HDL progr + RS progr + OGIS bas + CLIm bas + $HbA_{1c}$ bas + GS bas + liver fat bas.
Model (7): $HbA_{1c}$ progression rate = Sex + Age bas + center + OGIS progr + CLIm progr + GS progr + TG progr + HDL progr + RS progr + OGIS bas + CLIm bas + $HbA_{1c}$ bas + GS bas + visceral fat bas.
Model (8): Model (6), with different *N* (see last column).
Model (9): Model (7), with different *N* (see last column). This is the model in Figure 1, panel B.
* *N* = 320 for columns Visceral fat bas and Liver fat bas.
OGIS: insulin sensitivity; CLIm: mixed meal test insulin clearance; GS: $\beta$-cell glucose sensitivity; TG: fasting triacylglycerol; HDL: fasting HDL-cholesterol; RS: $\beta$-cell rate sensitivity; BMI: body mass index; progr: progression rate; bas: baseline value; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

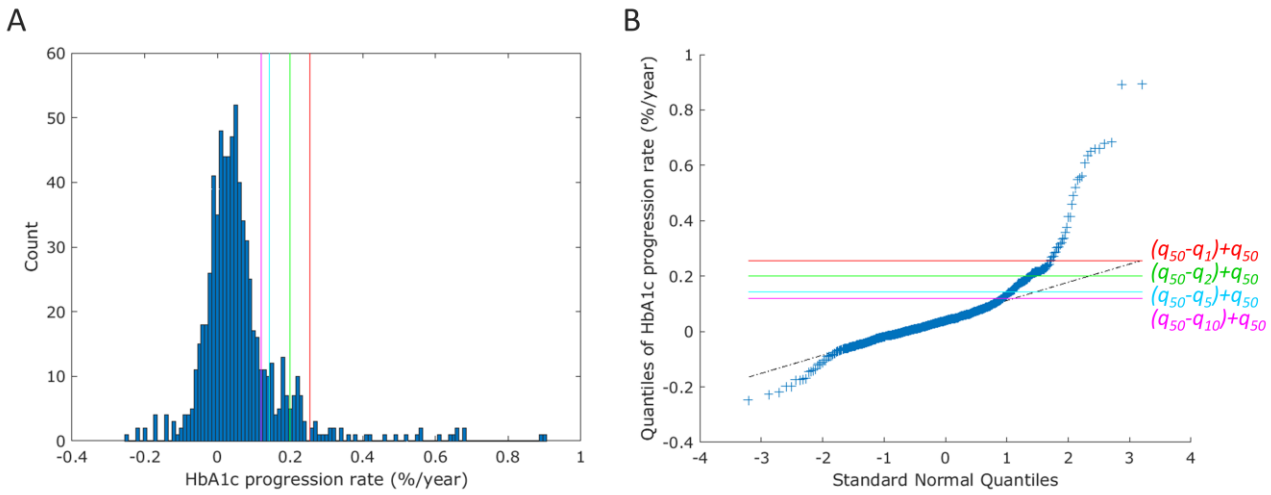



**Figure S1.** Distribution of the estimated individual progression rates of $HbA_{1c}$ (*N*=732), adjusted for changes in BMI and anti-diabetic medications. Panel A: histogram. Panel B: quantile-quantile plot. In both panels, four straight solid lines show four different thresholds used to split subjects into average and fast progressors. The thresholds were computed as $(q_{50} - q_n) + q_{50}$, where $q_n$ and $q_{50}$ are the $n^{th}$ and $50^{th}$ quantiles of the distribution: the threshold used in the main text (n=1) is shown in red, three less conservative thresholds (n=2, 5 and 10) are shown in green, light blue and purple, respectively.

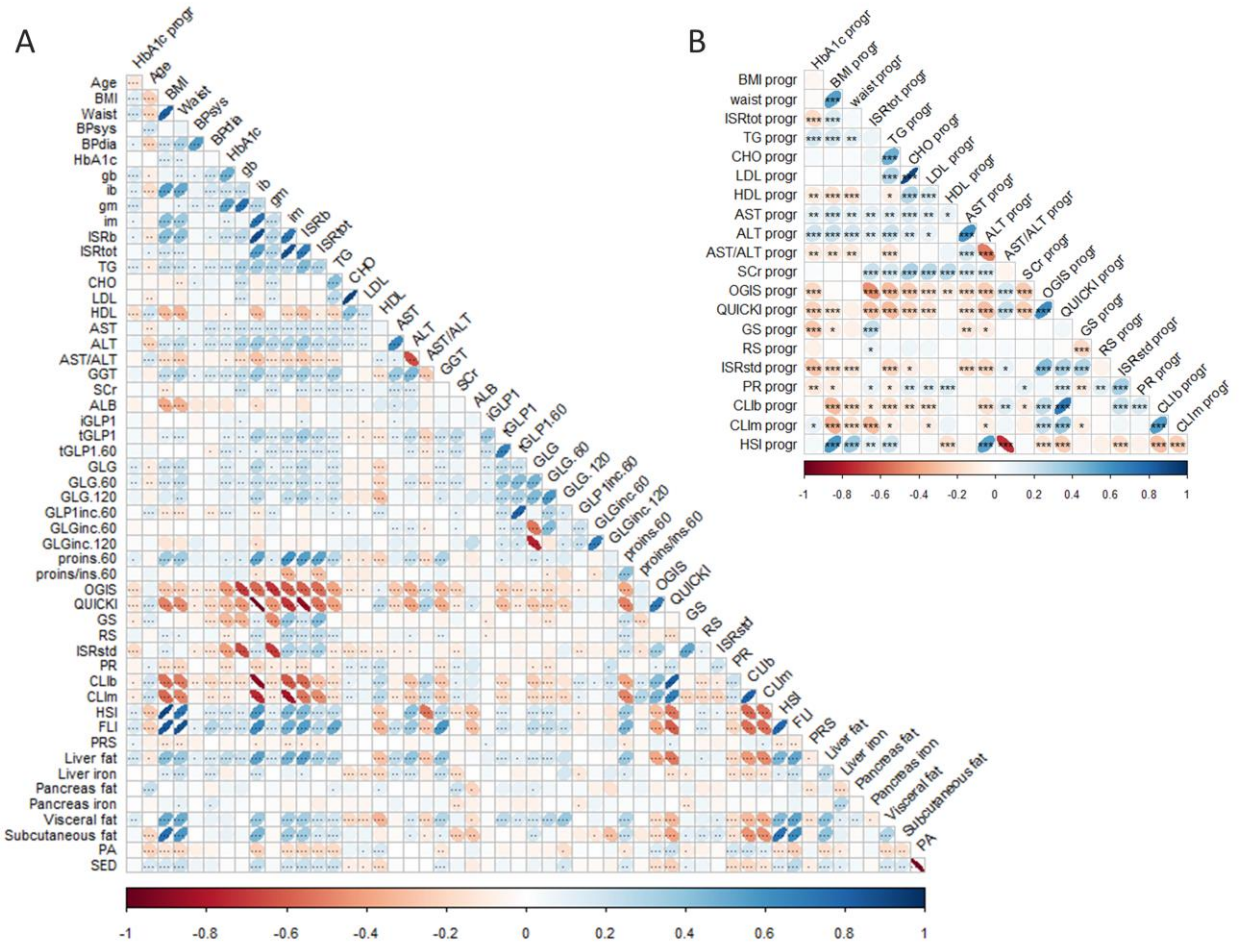
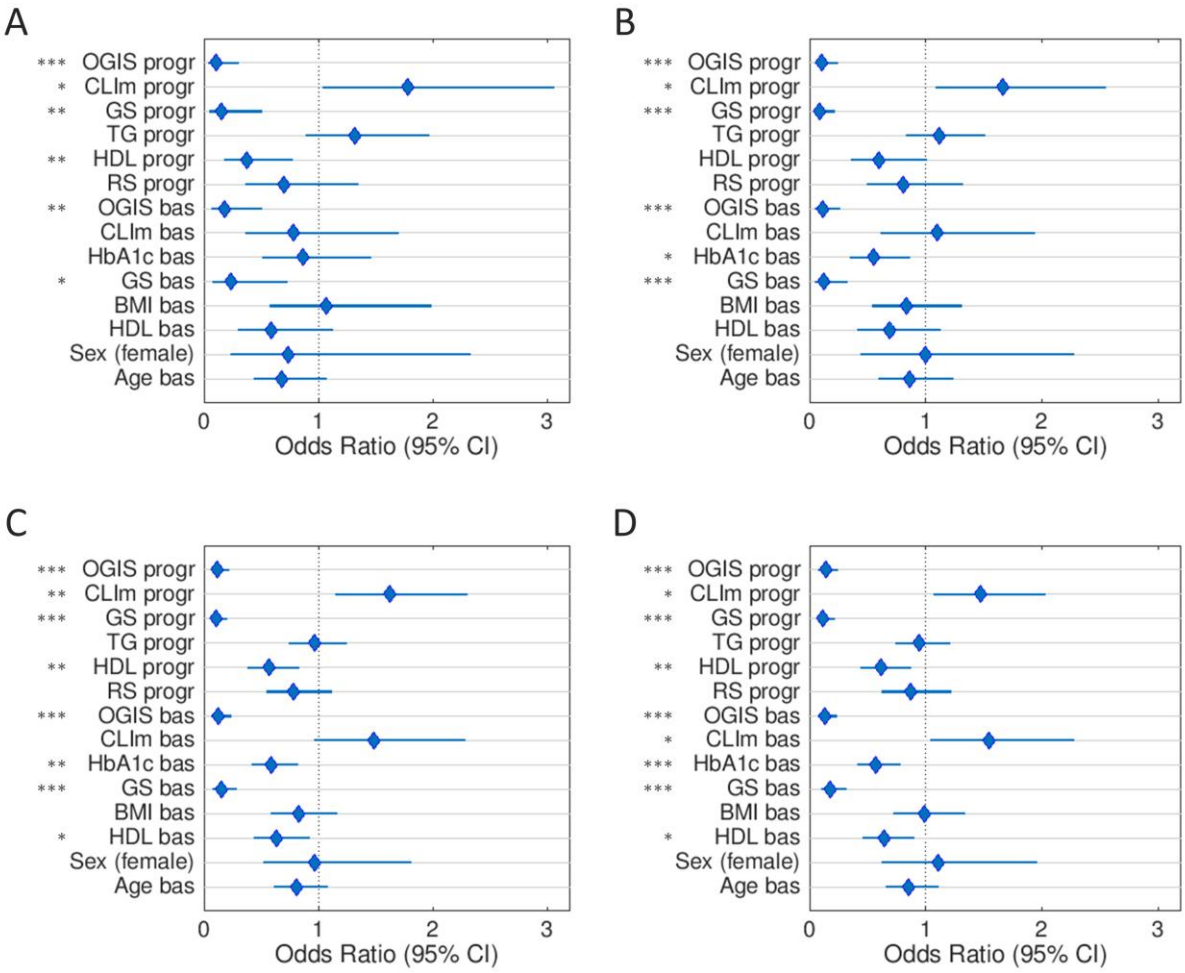



**Figure S2.** Pairwise correlation matrixes of the variables considered in this study (diet variables excluded as none was associated with HbA1c progression rate). Panel A: pairwise correlations among baseline values of the traits and $HbA_{1c}$ progression rates. Panel B: pairwise correlations among all the estimated progression rates. Correlations with $HbA_{1c}$ progression rates are displayed in the first columns of both panels. Fill color represents Spearman correlation coefficient, where positivity is denoted by red fill, negativity by blue fill, and magnitude by color intensity (see color bars) and by elliptic shape. BMI: body mass index; BPsys: systolic blood pressure; BPdia: diastolic blood pressure; gb: fasting glucose; ib: fasting insulin; gm: mean mixed meal test (MMTT) glucose; im: mean MMTT insulin; ISRb: fasting insulin secretion (ISR); ISRtot: total MMTT insulin secretion; TG: fasting triacylglycerol; CHO: fasting total cholesterol; LDL: fasting LDL-cholesterol; HDL: fasting HDL-cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AST/ALT: AST/ALT ratio; GGT: gamma-glutamyl transferase; SCr: serum creatinine; ALB: serum albumin; iGLP1: fasting intact glucagon-like peptide-1 (GLP-1); tGLP1: fasting total GLP-1; tGLP1.60: 1-h total GLP-1; GLG: fasting glucagon; GLG.60: 1-h glucagon; GLG.120: 2-h glucagon; GLP1inc.60: 1-h GLP-1 increment; GLGinc.60: 1-h glucagon increment; GLGinc.120: 2-h glucagon increment; proins.60: 1-h intact proinsulin; proins/ins.60: 1-h intact proinsulin to insulin ratio; OGIS insulin sensitivity; QUICKI: fasting insulin sensitivity; GS: $\beta$-cell glucose sensitivity; RS: $\beta$-cell rate sensitivity; ISRstd: insulin secretion rate at 8 mmol/l glucose; PR: potentiation factor ratio; CLIb: fasting insulin clearance; CLIm: MMTT insulin clearance; HSI: hepatic steatosis index; FLI: fatty liver index; PRS: polygenic risk score; PA: physical activity intensity; SED: sedentary behavior; progr: progression rate; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.




| Panel | Threshold on $HbA_{1c}$ progression rate (%/year, mmol $mol^{-1}$ $year^{-1}$) | Number of fast progressors | AUROC [95% CI] | Sensitivity | Specificity | Accuracy |
|---|---|---|---|---|---|---|
| A | 0.255, 2.79 | 33 | 0.94 [0.87-0.97] | 0.84 | 0.93 | 0.92 |
| B | 0.200, 2.19 | 61 | 0.93 [0.88-0.95] | 0.86 | 0.88 | 0.88 |
| C | 0.143, 1.56 | 110 | 0.91 [0.87-0.93] | 0.87 | 0.83 | 0.83 |
| D | 0.121, 1.32 | 131 | 0.89 [0.85-0.92] | 0.81 | 0.84 | 0.84 |

**Figure S3.** Odds ratios ± 95% confidence interval (CI) from the multivariable logistic analysis of fast *vs* average $HbA_{1c}$ progressors, using different thresholds between the two groups. The independent variables are those identified by multivariable linear analysis of $HbA_{1c}$ progression, excluding MRI variables ($N$=625). Panels A to D refer to progressively lower thresholds as shown in Figure S1 and in the summary table at the bottom. Age and HDL were log-transformed. Values for sensitivity, specificity and accuracy were derived via maximization of balanced accuracy. OGIS: insulin sensitivity; CLIm: mixed meal test insulin clearance; GS: $\beta$-cell glucose sensitivity; TG: fasting triacylglycerol; HDL: fasting HDL-cholesterol; RS: $\beta$-cell rate sensitivity; BMI: body mass index; progr: progression rate; bas: baseline value; AUROC: area under the receiver operating curve; *: $p$<0.05; **: $p$<0.01; ***: $p$<0.001.