

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Lyssenko V, Jonsson A, Almgren P, et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med* 2008;359:2220-32.

## Supplementary Appendix

### SUPPLEMENTARY METHODS

In the Malmö Preventive Project (MPP), 33,346 Swedish subjects (22,444 men and 10,902 women; mean age 49 years, 24.5% with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) from the city of Malmö in southern Sweden participated in a health screening during 1974-1992 (with a 71% attendance rate; Fig. 1A). Men were included from 1974-1990 and women, from 1980-1992.<sup>1</sup> All participants underwent a physical examination, and each had blood drawn for measurements of fasting blood glucose and lipid concentrations. In addition, 18,900 consecutive persons also had an oral glucose tolerance test (OGTT). Information about lifestyle factors and medical history was obtained from questionnaires. Of those persons participating in the initial screening, 4,931 have died, and 551 are lost to follow-up. Twenty-five thousand eligible participants were invited to a re-screening visit during 2002-2006; this included a physical examination and fasting blood samples for measurements of plasma glucose and lipids. Of those invited, 17,284 persons participated in the re-screening; of these 1,223 were excluded because of incomplete medical information or lack of a DNA sample (or type 2 diabetes at baseline). Thereby, 16,061 non-diabetic subjects, 2,063 of whom developed type 2 diabetes during follow-up, were included in the current analyses. Diagnosis of diabetes was confirmed from patient records or based upon a fasting plasma glucose concentration equal to or greater than 7.0 mmol/l (126 mg/dl).

The Botnia study started in 1990 on the West coast of Finland with the aim of identifying genes increasing susceptibility to type 2 diabetes in members of families with type 2 diabetes.<sup>2</sup> The prospective part included 2,770 non-diabetic family members and/or their spouses (1,263 men and 1,507 women, mean age 45 years), 138 of whom developed type 2 diabetes during a 7.6 year (median) follow-up period (Fig.1B).<sup>3,4</sup> All subjects were given information about exercise and healthy diet and underwent a repeat OGTT at 2-3 year intervals.

The diagnosis of diabetes was confirmed from patient records or based on a fasting plasma glucose concentration equal to or greater than 7.0 mmol/l (126.0 mg/dl) and/or 2 hr glucose greater than 11.0 mmol/l (200.0 mg/dl). Two thousand three hundred twenty eight non-diabetic participants also had serum insulin concentrations measured at baseline and during follow-up.

#### References:

1. Berglund G, Nilsson P, Eriksson KF, et al. Long-term outcome of the Malmo preventive project: mortality and cardiovascular morbidity. *J Intern Med* 2000;247(1):19-29.
2. Groop L, Forsblom C, Lehtovirta M, et al. Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects. *Diabetes* 1996;45(11):1585-93.
3. Lyssenko V, Almgren P, Anevski D, et al. Predictors of and longitudinal changes in insulin sensitivity and secretion preceding onset of type 2 diabetes. *Diabetes* 2005;54(1):166-74.
4. Lyssenko V, Almgren P, Anevski D, et al. Genetic prediction of future type 2 diabetes. *PLoS medicine* 2005;2(12):e345.

## **SUPPLEMENTARY TABLES**

**Supplementary Table 1A. Clinical characteristics of subjects at baseline in Malmö and Botnia prospective studies.**

**Supplementary Table 1B. Spearman correlations between different clinical factors in the Malmö cohort at baseline.**

**Supplementary Table 1C. Spearman correlations between different clinical factors in the Botnia cohort at baseline.**

**Supplementary Table 2A. Clinical factors predicting type 2 diabetes at baseline in Malmö and Botnia prospective studies (univariate regression analysis): adjusted for body mass index.**

**Supplementary Table 2B. Clinical factors predicting type 2 diabetes in subjects with normal glucose tolerance and with impaired fasting glucose or impaired glucose tolerance at baseline in the Malmö study (univariate regression analysis).**

**Supplementary Table 2C. Comparison of baseline clinical factors predicting type 2 diabetes in Malmö and Botnia prospective studies between subjects from the highest and lowest quartiles (univariate regression analysis).**

**Supplementary Table 2D. Comparison of baseline clinical factors predicting type 2 diabetes in Malmö and Botnia prospective studies between subjects from the highest and lowest quartiles (univariate regression analysis): adjusted for body mass index.**

**Supplementary Table 2E. Comparison of baseline clinical factors predicting progression from normal glucose tolerance and impaired fasting glucose or impaired glucose tolerance to type 2 diabetes in the Malmö study between subjects from the highest and lowest quartiles (univariate regression analysis): adjusted for body mass index.**

**Supplementary Table 3. Genetic factors predicting type 2 diabetes in subjects with normal glucose tolerance and with impaired fasting glucose or impaired glucose tolerance at baseline in the Malmö prospective study.**

**Supplementary Table 4. Area under the ROC curves (C Statistics) for different models predicting type 2 diabetes.**

**Supplementary Table 5. Comparison of predicted risks of type 2 diabetes with and without genetic risk factors using reclassification approach.**

**Supplementary Table 6. Area under the ROC curves (C Statistics) for different models predicting type 2 diabetes in quintiles of duration of follow-up.**

**Supplementary Table 1A. Clinical characteristics of subjects at baseline in Malmö and Botnia prospective studies.**

|  | Malmö  |                          | Botnia |                          |
|--|--------|--------------------------|--------|--------------------------|
|  | Number |                          | Number |                          |
| Male sex (%)   | 10416  | 64.9                     | 1260   | 45.5                     |
| Age (years)  | 16061  | 45.5 ± 6.9               | 2759   | 44.9 ± 14.2              |
| First-degree family history of diabetes (%)                            | 1885   | 14.5                     | 2261   | 82.7                     |
| Current smoking status (%)   | 5981   | 38.2                     | 983    | 38.1                     |
| Impaired fasting glucose level (%)                                     | 1980   | 12.3                     | 194    | 7.0                      |
| Impaired glucose tolerance (%)   | 1507   | 9.4                      | 357    | 12.9                     |
| Both impaired fasting glucose level and impaired glucose tolerance (%) | 364    | 2.3                      | 125    | 4.5                      |
| Body mass index (kg/height <sup>2</sup> )                              | 16055  | 24.3 (3.3)               | 2746   | 25.6 (4.1)               |
| Waist (cm)   |        |                          |        |                          |
| Men  | -      | -                        | 1216   | 92.9 (10.1)              |
| Women  | -      | -                        | 1460   | 82.3 (11.5)              |
| Blood pressure (mmHg)  |        |                          |        |                          |
| Systolic   | 16060  | 127.2 (14.3)             | 2690   | 128.3 (17.8)             |
| Diastolic  | 16060  | 84.0 (8.9)               | 2689   | 78.6 (10.6)              |
| Triglycerides (mmol/L) / (mg/dl)                                       | 16036  | 1.10 [0.7] / 97.9 [62.3] | 2517   | 1.07 [0.7] / 95.2 [62.3] |
| γ-glutamyltransferase (U/L)  | 16024  | 21.6 [16.2]              | 2009   | 20.0 [16.0]              |
| Aspartate aminotransferase (U/L)                                       | 14487  | 21.0 [6.6]               | 2672   | 23.0 [9.0]               |
| Alanine aminotransferase (U/L)   | 14493  | 18.6 [10.8]              | -      | -                        |
| Apolipoprotein A-I (mg/L)  | 5191   | 130.0 [35.0]             | 2518   | 137.0 [29.0]             |
| Insulin sensitivity index  | 2814   | 164.7 [170.4]            | 2629   | 105.7 [74.5]             |
| Insulin resistance index   | 3078   | 1.0 [1.2]                | 2629   | 0.9 [0.6]                |
| Corrected insulin response   | 1601   | 148.8 [127.4]            | 2524   | 133.9 [135.8]            |
| Disposition index  | 1583   | 23393 [27302]            | 2524   | 13290 [15351]            |
| Follow-up time in the study (years)                                    | 16061  | 24.8 [19.8]              | 2770   | 7.6 [5.4]                |
| Converters to diabetes (%)   | 2063   | 12.8                     | 138    | 5.0                      |

Data are mean (SD) or median [IQR]. To convert the values from millimoles per liter to milligrams per deciliter, multiply triglycerides by 89. The body-mass index is the weight in kilograms divided by the square of the height in meters.

**Supplementary Table 1B. Spearman correlations between different baseline clinical factors in the Malmö cohort at baseline.**

|         |   | SEX     | AGE     | FH       | Smoking | BMI     | SBP     | DBP     | TG      | GT      | ASAT    | ALAT    | APOA    | ISI     | HOMA-IR | CIR     | DI      |
|---------|---|---------|---------|----------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| SEX     | R | 1       | 0.534   | 0.068    | 0.095   | -0.103  | -0.050  | -0.151  | -0.275  | -0.446  | -0.178  | -0.166  | 0.077   | 0.002   | -0.164  | -0.093  | -0.100  |
|         | P | -       | <0.0001 | <0.0001  | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.92    | <0.0001 | <0.001  | <0.0001 |
| AGE     | R | 0.534   | 1       | 0.070    | 0.105   | 0.102   | 0.151   | 0.074   | -0.108  | -0.177  | -0.010  | 0.007   | -0.078  | -0.103  | 0.119   | 0.069   | -0.099  |
|         | P | <0.0001 | -       | <0.0001  | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.23    | 0.40    | <0.0001 | <0.0001 | <0.0001 | <0.01   | <0.0001 |
| FH      | R | 0.068   | 0.070   | 1        | 0.026   | 0.046   | -0.002  | -0.021  | 0.001   | -0.009  | -0.004  | 0.026   | -0.008  | -0.065  | 0.029   | -0.079  | -0.122  |
|         | P | <0.0001 | <0.0001 | -        | <0.01   | <0.0001 | 0.84    | <0.05   | 0.88    | 0.29    | 0.71    | <0.01   | 0.66    | <0.001  | 0.11    | <0.01   | <0.0001 |
| Smoking | R | 0.095   | 0.105   | 0.026    | 1       | 0.104   | 0.170   | 0.173   | -0.140  | -0.078  | 0.076   | 0.064   | 0.059   | -0.113  | 0.003   | 0.029   | -0.080  |
|         | P | <0.0001 | <0.0001 | <0.01    | -       | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.87    | 0.25    | <0.01   |
| BMI     | R | -0.103  | 0.102   | 0.046    | 0.104   | 1       | 0.275   | 0.281   | 0.296   | 0.264   | 0.188   | 0.334   | -0.074  | -0.344  | 0.269   | 0.149   | -0.173  |
|         | P | <0.0001 | <0.0001 | <0.0001  | <0.0001 | -       | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| SBP     | R | -0.050  | 0.151   | -0.002   | 0.170   | 0.275   | 1       | 0.693   | 0.151   | 0.164   | 0.160   | 0.181   | 0.044   | -0.230  | 0.172   | -0.050  | -0.215  |
|         | P | <0.0001 | <0.0001 | 0.84     | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.01   | <0.0001 | <0.0001 | <0.05   | <0.0001 |
| DBP     | R | -0.151  | 0.074   | -0.021   | 0.173   | 0.281   | 0.693   | 1       | 0.194   | 0.212   | 0.168   | 0.186   | 0.012   | -0.205  | 0.148   | 0.032   | -0.133  |
|         | P | <0.0001 | <0.0001 | <0.05    | <0.0001 | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.37    | <0.0001 | <0.0001 | 0.20    | <0.0001 |
| TG      | R | -0.275  | -0.108  | 0.001    | -0.140  | 0.296   | 0.151   | 0.194   | 1       | 0.371   | 0.134   | 0.226   | -0.106  | -0.260  | 0.229   | 0.111   | -0.102  |
|         | P | <0.0001 | <0.0001 | 0.88     | <0.0001 | <0.0001 | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| GT      | R | -0.446  | -0.177  | -0.009   | -0.078  | 0.264   | 0.164   | 0.212   | 0.371   | 1       | 0.367   | 0.492   | 0.013   | -0.222  | 0.241   | 0.117   | -0.106  |
|         | P | <0.0001 | <0.0001 | 0.29     | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 | 0.37    | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| ASAT    | R | -0.178  | -0.010  | -0.004   | 0.076   | 0.188   | 0.160   | 0.168   | 0.134   | 0.367   | 1       | 0.609   | 0.082   | -0.064  | 0.0884  | 0.045   | -0.034  |
|         | P | <0.0001 | 0.23    | 0.71     | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 | <0.01   | <0.0001 | 0.17    | 0.31    |
| ALAT    | R | -0.166  | 0.007   | 0.026    | 0.064   | 0.334   | 0.181   | 0.186   | 0.226   | 0.492   | 0.609   | 1       | -0.031  | -0.249  | 0.242   | 0.108   | -0.138  |
|         | P | <0.0001 | 0.40    | 0.0061   | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | -       | <0.05   | <0.0001 | <0.0001 | <0.01   |
| APOA    | R | 0.077   | -0.078  | -0.008   | 0.059   | -0.074  | 0.044   | 0.012   | -0.106  | 0.013   | 0.082   | -0.031  | 1       | 0.110   | -0.116  | -0.312  | -0.307  |
|         | P | <0.0001 | <0.0001 | 0.66     | <0.0001 | <0.0001 | <0.01   | 0.37    | <0.0001 | 0.37    | <0.0001 | <0.05   | -       | <0.001  | <0.0001 | 0.053   | 0.065   |
| ISI     | R | 0.002   | -0.103  | -0.065   | -0.113  | -0.344  | -0.230  | -0.205  | -0.260  | -0.222  | -0.064  | -0.249  | 0.110   | 1       | -0.856  | -0.221  | 0.649   |
|         | P | 0.92    | <0.0001 | <0.001   | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.01   | <0.0001 | <0.001  | -       | <0.0001 | <0.0001 | <0.0001 |
| HOMA-IR | R | -0.164  | 0.119   | 0.029    | 0.003   | 0.269   | 0.172   | 0.148   | 0.229   | 0.241   | 0.088   | 0.242   | -0.116  | -0.856  | 1       | 0.288   | -0.481  |
|         | P | <0.0001 | <0.0001 | 0.1055   | 0.87    | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 |
| CIR     | R | -0.093  | 0.069   | -0.07908 | 0.029   | 0.149   | -0.050  | 0.032   | 0.111   | 0.117   | 0.045   | 0.108   | -0.312  | -0.221  | 0.288   | 1       | 0.552   |
|         | P | <0.001  | <0.01   | <0.01    | 0.25    | <0.0001 | <0.05   | 0.20    | <0.0001 | <0.0001 | 0.17    | <0.01   | 0.053   | <0.0001 | <0.0001 | -       | <0.0001 |
| DI      | R | -0.100  | -0.099  | -0.12212 | -0.080  | -0.173  | -0.215  | -0.133  | -0.102  | -0.106  | -0.034  | -0.138  | -0.307  | 0.649   | -0.481  | 0.552   | 1       |
|         | P | <0.0001 | <0.0001 | <0.0001  | <0.01   | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.31    | <0.0001 | 0.065   | <0.0001 | <0.0001 | <0.0001 | -       |

**Supplementary Table 1C. Spearman correlations between different baseline clinical factors in the Botnia cohort at baseline.**

|         |   | SEX     | AGE     | FH      | Smoking | BMI     | WAIST   | SBP     | DBP     | TG      | GT      | ASAT    | APOA1   | ISI     | HOMA_IR | CIR     | DI      |
|---------|---|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| SEX     | R | 1       | 0.060   | -0.011  | -0.300  | -0.102  | -0.470  | -0.072  | -0.075  | -0.171  | -0.356  | -0.304  | 0.334   | 0.037   | -0.032  | 0.191   | 0.191   |
|         | P | -       | <0.01   | 0.57    | <0.0001 | <0.0001 | <0.0001 | <0.001  | <0.001  | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.057   | 0.098   | <0.0001 | <0.0001 |
| AGE     | R | 0.060   | 1       | -0.127  | -0.068  | 0.318   | 0.270   | 0.490   | 0.374   | 0.244   | 0.097   | 0.043   | 0.147   | -0.195  | 0.062   | -0.117  | -0.212  |
|         | P | <0.01   | -       | <0.0001 | <0.001  | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.05   | <0.0001 | <0.0001 | <0.01   | <0.0001 | <0.0001 |
| FH      | R | -0.011  | -0.127  | 1       | 0.007   | -0.013  | -0.002  | -0.001  | 0.006   | 0.006   | -0.043  | -0.077  | -0.0005 | -0.025  | 0.012   | -0.029  | -0.053  |
|         | P | 0.57    | <0.0001 | -       | 0.72    | 0.50    | 0.92    | 0.94    | 0.77    | 0.75    | 0.057   | <0.0001 | 0.98    | 0.21    | 0.55    | 0.15    | <0.01   |
| Smoking | R | -0.300  | -0.068  | 0.007   | 1       | 0.070   | 0.172   | -0.048  | -0.040  | 0.118   | 0.135   | -0.002  | -0.156  | -0.005  | 0.011   | -0.111  | -0.110  |
|         | P | <0.0001 | <0.001  | 0.72    | -       | <0.001  | <0.0001 | <0.05   | <0.05   | <0.0001 | <0.0001 | 0.91    | <0.0001 | 0.82    | 0.58    | <0.0001 | <0.0001 |
| BMI     | R | -0.102  | 0.318   | -0.013  | 0.070   | 1       | 0.783   | 0.352   | 0.377   | 0.393   | 0.290   | 0.107   | -0.144  | -0.464  | 0.431   | 0.015   | -0.289  |
|         | P | <0.0001 | <0.0001 | 0.50    | <0.001  | -       | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.47    | <0.0001 |
| WAIST   | R | -0.470  | 0.270   | -0.002  | 0.172   | 0.783   | 1       | 0.341   | 0.364   | 0.443   | 0.423   | 0.221   | -0.281  | -0.444  | 0.419   | -0.070  | -0.358  |
|         | P | <0.0001 | <0.0001 | 0.92    | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.001  | <0.0001 |
| SBP     | R | -0.072  | 0.490   | -0.001  | -0.048  | 0.352   | 0.341   | 1       | 0.713   | 0.255   | 0.149   | 0.087   | 0.046   | -0.288  | 0.200   | -0.061  | -0.241  |
|         | P | <0.001  | <0.0001 | 0.94    | <0.05   | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.05   | <0.0001 | <0.0001 | <0.01   | <0.0001 |
| DBP     | R | -0.075  | 0.374   | 0.006   | -0.040  | 0.377   | 0.364   | 0.713   | 1       | 0.238   | 0.225   | 0.092   | 0.046   | -0.225  | 0.173   | -0.063  | -0.200  |
|         | P | <0.001  | <0.0001 | 0.77    | <0.05   | <0.0001 | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 | <0.0001 | <0.05   | <0.0001 | <0.0001 | <0.01   | <0.0001 |
| TG      | R | -0.171  | 0.244   | 0.006   | 0.118   | 0.393   | 0.443   | 0.255   | 0.238   | 1       | 0.294   | 0.099   | -0.159  | -0.458  | 0.394   | 0.026   | -0.273  |
|         | P | <0.0001 | <0.0001 | 0.75    | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.21    | <0.0001 |
| GT      | R | -0.356  | 0.097   | -0.043  | 0.135   | 0.290   | 0.423   | 0.149   | 0.225   | 0.294   | 1       | 0.363   | -0.086  | -0.271  | 0.301   | -0.075  | -0.257  |
|         | P | <0.0001 | <0.0001 | 0.057   | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | -       | <0.0001 | <0.001  | <0.0001 | <0.0001 | <0.01   | <0.0001 |
| ASAT    | R | -0.304  | 0.043   | -0.077  | -0.002  | 0.107   | 0.221   | 0.087   | 0.092   | 0.099   | 0.363   | 1       | -0.039  | -0.064  | 0.105   | -0.089  | -0.137  |
|         | P | <0.0001 | <0.05   | <0.0001 | 0.91    | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | -       | 0.051   | <0.01   | <0.0001 | <0.0001 | <0.0001 |
| APOA1   | R | 0.334   | 0.147   | -0.0005 | -0.156  | -0.144  | -0.281  | 0.0464  | 0.046   | -0.159  | -0.086  | -0.039  | 1       | 0.144   | -0.177  | -0.051  | 0.066   |
|         | P | <0.0001 | <0.0001 | 0.98    | <0.0001 | <0.0001 | <0.0001 | <0.05   | <0.05   | <0.0001 | <0.001  | 0.051   | -       | <0.0001 | <0.0001 | <0.05   | <0.01   |
| ISI     | R | 0.037   | -0.195  | -0.025  | -0.005  | -0.464  | -0.444  | -0.288  | -0.225  | -0.458  | -0.271  | -0.064  | 0.144   | 1       | -0.854  | -0.164  | 0.480   |
|         | P | 0.057   | <0.0001 | 0.21    | 0.82    | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.01   | <0.0001 | -       | <0.0001 | <0.0001 | <0.0001 |
| HOMA-IR | R | -0.032  | 0.062   | 0.012   | 0.011   | 0.431   | 0.419   | 0.200   | 0.173   | 0.394   | 0.301   | 0.105   | -0.177  | -0.854  | 1       | 0.211   | -0.374  |
|         | P | 0.098   | <0.01   | 0.55    | 0.58    | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | -       | <0.0001 | <0.0001 |
| CIR     | R | 0.191   | -0.117  | -0.029  | -0.111  | 0.015   | -0.070  | -0.061  | -0.063  | 0.026   | -0.075  | -0.089  | -0.051  | -0.164  | 0.211   | 1       | 0.747   |
|         | P | <0.0001 | <0.0001 | 0.15    | <0.0001 | 0.47    | <0.001  | <0.01   | <0.01   | 0.21    | <0.01   | <0.0001 | <0.05   | <0.0001 | <0.0001 | -       | <0.0001 |
| DI      | R | 0.191   | -0.212  | -0.053  | -0.110  | -0.289  | -0.358  | -0.241  | -0.200  | -0.273  | -0.257  | -0.137  | 0.066   | 0.480   | -0.374  | 0.747   | 1       |
|         | P | <0.0001 | <0.0001 | <0.01   | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.01   | <0.0001 | <0.0001 | <0.0001 | -       |

**Supplementary Table 2A. Clinical factors predicting type 2 diabetes at baseline in Malmö and Botnia prospective studies (univariate regression analysis): adjusted for body mass index.**

|  | Malmö                  |                        |                | Botnia                 |                       |                |
|--|------------------------|------------------------|----------------|------------------------|-----------------------|----------------|
|  | Odds ratio<br>(95% CI) | P value                | R <sup>2</sup> | Odds ratio<br>(95% CI) | P value               | R <sup>2</sup> |
| Age, per SD  | 1.02 (0.96-1.08)       | $5.9 \times 10^{-1}$   |                | 1.69 (1.038-2.08)      | $2.7 \times 10^{-7}$  |                |
| First-degree family history of diabetes                            | 1.61 (1.40-1.85)       | $2.5 \times 10^{-11}$  | 0.061          | 2.15 (1.21-3.81)       | $9.0 \times 10^{-3}$  | 0.121          |
| Current smoking status   | 1.51 (1.37-1.67)       | $3.2 \times 10^{-16}$  | 0.059          | 1.12 (0.69-1.80)       | $6.5 \times 10^{-1}$  | 0.116          |
| Impaired fasting glucose level                                     | 2.23 (1.97-2.53)       | $3.3 \times 10^{-36}$  | -              | 3.34 (1.92-5.81)       | $2.3 \times 10^{-5}$  | -              |
| Impaired glucose tolerance   | 1.66 (1.39-1.97)       | $4.8 \times 10^{-9}$   | -              | 3.11 (1.92-5.02)       | $1.1 \times 10^{-6}$  | -              |
| Both impaired fasting glucose level and impaired glucose tolerance | 4.06 (3.18-5.18)       | $3.3 \times 10^{-32}$  | -              | 5.67 (3.26-9.86)       | $4.5 \times 10^{-11}$ | -              |
| Increased body mass index, per SD                                  | 1.84 (1.76-1.93)       | $2.1 \times 10^{-153}$ | 0.057          | 1.84 (1.57-2.16)       | $5.0 \times 10^{-13}$ | 0.107          |
| Increased waist, per SD  | -                      | -                      |                | 1.98 (1.41-2.78)       | $9.4 \times 10^{-5}$  | 0.126          |
| Increased blood pressure, per SD                                   |                        |                        |                |                        |                       |                |
| Systolic   | 1.17 (1.12-1.23)       | $1.3 \times 10^{-10}$  | 0.059          | 1.37 (1.14-1.65)       | $1.4 \times 10^{-3}$  | 0.120          |
| Diastolic  | 1.21 (1.15-1.27)       | $4.8 \times 10^{-14}$  | 0.060          | 1.27 (1.05-1.54)       | $2.1 \times 10^{-2}$  | 0.115          |
| Increased triglycerides, per SD                                    | 1.46 (1.39-1.54)       | $1.8 \times 10^{-48}$  | 0.070          | 1.33 (1.11-1.60)       | $2.9 \times 10^{-3}$  | 0.107          |
| Increased $\gamma$ -glutamyltransferase, per SD                    | 1.36 (1.30-1.43)       | $1.1 \times 10^{-34}$  | 0.065          | 1.30 (1.08-1.56)       | $5.9 \times 10^{-3}$  | 0.115          |
| Increased aspartate aminotransferase, per SD                       | 1.17 (1.12-1.23)       | $3.9 \times 10^{-10}$  | 0.060          | 0.94 (0.78-1.13)       | $5.3 \times 10^{-1}$  | 0.105          |
| Increased alanine aminotransferase, per SD                         | 1.40 (1.33-1.48)       | $1.4 \times 10^{-37}$  | 0.068          | -                      | -                     | -              |
| Increased apolipoprotein A-I, per SD                               | 0.82 (0.75-0.89)       | $3.4 \times 10^{-6}$   | 0.051          | 0.81 (0.67-0.99)       | $2.8 \times 10^{-2}$  | 0.102          |
| Increased insulin sensitivity index, per SD                        | 0.69 (0.62-0.77)       | $1.9 \times 10^{-10}$  | 0.058          | 0.51 (0.42-0.61)       | $1.5 \times 10^{-11}$ | 0.160          |
| Increased insulin resistance index, per SD                         | 1.29 (1.16-1.43)       | $1.9 \times 10^{-6}$   | 0.049          | 1.70 (1.40-2.05)       | $2.0 \times 10^{-6}$  | 0.140          |
| Decreased corrected insulin response, per SD                       | 1.44 (1.24-1.66)       | $9.8 \times 10^{-7}$   | 0.063          | 1.60 (1.30-1.97)       | $4.5 \times 10^{-5}$  | 0.135          |
| Decreased disposition index, per SD                                | 1.98 (1.69-2.31)       | $1.4 \times 10^{-17}$  | 0.095          | 3.01 (2.34-3.88)       | $2.3 \times 10^{-17}$ | 0.210          |

Risk is presented as change in one unit of SD (standard deviation). Nagelkerke R-square (R<sup>2</sup>) is for the full model, denotes percent of type 2 diabetes risk explained by risk factors. The odds ratios for risk of developing type 2 diabetes and R<sup>2</sup> and are calculated using logistic regression analyses adjusted for age at participation, body mass index (apart from body mass index) and sex.

**Supplementary Table 2B. Clinical factors predicting type 2 diabetes in subjects with normal glucose tolerance or with impaired fasting glucose or impaired glucose tolerance at baseline in the Malmö prospective study (univariate regression analysis).**

|   | From normal glucose tolerance to type 2 diabetes |                     |                       |                | From impaired fasting glucose or impaired glucose tolerance to type 2 diabetes |                     |                       |                |
|---|--|---------------------|-----------------------|----------------|--|---------------------|-----------------------|----------------|
|   | Number   | Odds ratio (95% CI) | P value               | R <sup>2</sup> | Number   | Odds ratio (95% CI) | P value               | R <sup>2</sup> |
| Age, per SD                                     | 12186  | 1.10 (1.02-1.18)    | $1.0 \times 10^{-2}$  | -              | 3817   | 1.14 (1.02-1.28)    | $2.6 \times 10^{-2}$  | -              |
| First-degree family history of diabetes         | 9885   | 1.45 (1.21-1.74)    | $6.0 \times 10^{-5}$  | 0.048          | 3082   | 1.81 (1.44-2.27)    | $4.2 \times 10^{-7}$  | 0.097          |
| Current smoking status                          | 11989  | 1.67 (1.48-1.89)    | $2.2 \times 10^{-16}$ | 0.049          | 3637   | 1.44 (1.20-1.71)    | $5.2 \times 10^{-5}$  | 0.081          |
| Increased body mass index, per SD               | 12181  | 1.79 (1.70-1.90)    | $5.0 \times 10^{-94}$ | 0.045          | 3816   | 1.75 (1.62-1.90)    | $3.9 \times 10^{-41}$ | 0.082          |
| Increased blood pressure, per SD                |  |                     |                       |                |  |                     |                       |                |
| Systolic  | 12181  | 1.26 (1.19-1.34)    | $1.2 \times 10^{-3}$  | 0.045          | 3816   | 1.27 (1.17-1.38)    | $2.7 \times 10^{-3}$  | 0.084          |
| Diastolic                                       | 12181  | 1.32 (1.25-1.40)    | $2.7 \times 10^{-6}$  | 0.046          | 3816   | 1.37 (1.27-1.49)    | $1.2 \times 10^{-5}$  | 0.087          |
| Increased triglycerides, per SD                 | 12164  | 1.63 (1.54-1.74)    | $5.6 \times 10^{-28}$ | 0.054          | 3808   | 1.59 (1.46-1.73)    | $2.3 \times 10^{-13}$ | 0.097          |
| Increased $\gamma$ -glutamyltransferase, per SD | 12155  | 1.47 (1.39-1.56)    | $9.3 \times 10^{-18}$ | 0.050          | 3806   | 1.54 (1.41-1.67)    | $3.9 \times 10^{-14}$ | 0.096          |
| Increased aspartate aminotransferase, per SD    | 10829  | 1.21 (1.14-1.29)    | $9.7 \times 10^{-4}$  | 0.045          | 3595   | 1.38 (1.27-1.50)    | $1.5 \times 10^{-7}$  | 0.091          |
| Increased alanine aminotransferase, per SD      | 10833  | 1.53 (1.44-1.63)    | $1.5 \times 10^{-16}$ | 0.050          | 3597   | 1.70 (1.56-1.85)    | $1.2 \times 10^{-18}$ | 0.104          |
| Increased apolipoprotein A-I, per SD            | 3857   | 0.74 (0.67-0.83)    | $4.1 \times 10^{-6}$  | 0.044          | 1323   | 0.82 (0.72-0.94)    | $2.0 \times 10^{-2}$  | 0.055          |
| Increased insulin sensitivity index, per SD     | 1961   | 0.66 (0.57-0.75)    | $2.1 \times 10^{-4}$  | 0.041          | 842  | 0.64 (0.54-0.76)    | $2.1 \times 10^{-3}$  | 0.106          |
| Increased insulin resistance index, per SD      | 2208   | 1.42 (1.25-1.60)    | $4.7 \times 10^{-4}$  | 0.040          | 859  | 1.45 (1.23-1.71)    | $7.9 \times 10^{-3}$  | 0.096          |
| Decreased corrected insulin response, per SD    | 1173   | 1.23 (1.04-1.46)    | $1.1 \times 10^{-3}$  | 0.077          | 423  | 1.03 (0.83-1.21)    | $8.3 \times 10^{-1}$  | 0.131          |
| Decreased disposition index, per SD             | 1158   | 1.87 (1.55-2.26)    | $1.5 \times 10^{-9}$  | 0.117          | 421  | 1.72 (1.35-2.21)    | $2.0 \times 10^{-4}$  | 0.162          |

Risk is presented for change in one unit of SD (standard deviation). Nagelkerke R-square (R<sup>2</sup>) is for the full model, denotes percent of type 2 diabetes risk explained by risk factors. The odds ratios for risk of developing type 2 diabetes and R<sup>2</sup> and are calculated using logistic regression analyses adjusted for age at participation and sex.

**Supplementary Table 2C. Comparison of baseline clinical factors predicting type 2 diabetes in Malmö and Botnia prospective studies between subjects from the highest and lowest quartiles (univariate regression analysis).**

|   | Malmö               |                         |                | Botnia              |                        |                |
|---|---------------------|-------------------------|----------------|---------------------|------------------------|----------------|
|   | Odds ratio (95% CI) | P value                 | R <sup>2</sup> | Odds ratio (95% CI) | P value                | R <sup>2</sup> |
| Increased body mass index (kg/height <sup>2</sup> ) | 4.94 (4.22-5.78)    | 8.2 × 10 <sup>-88</sup> | 0.079          | 9.29 (3.83-22.56)   | 8.5 × 10 <sup>-7</sup> | 0.132          |
| Increased waist (cm)                                | -                   | -                       | -              | 14.02 (5.75-32.21)  | 6.5 × 10 <sup>-9</sup> | 0.158          |
| Increased blood pressure (mmHg)                     |                     |                         |                |                     |                        |                |
| Systolic  | 2.36 (2.04-2.72)    | 1.2 × 10 <sup>-31</sup> | 0.034          | 4.87 (2.21-10.75)   | 8.7 × 10 <sup>-5</sup> | 0.098          |
| Diastolic   | 2.30 (2.02-2.63)    | 4.7 × 10 <sup>-35</sup> | 0.033          | 2.39 (1.31-4.36)    | 4.7 × 10 <sup>-3</sup> | 0.075          |
| Increased triglycerides (mmol/L)                    | 4.27 (3.64-5.01)    | 1.5 × 10 <sup>-70</sup> | 0.069          | 2.64 (1.42-4.93)    | 2.2 × 10 <sup>-3</sup> | 0.080          |
| Increased γ-glutamyltransferase (U/L)               | 3.27 (2.74-3.90)    | 4.4 × 10 <sup>-40</sup> | 0.060          | 3.24 (1.64-6.36)    | 6.7 × 10 <sup>-4</sup> | 0.076          |
| Increased aspartate aminotransferase (U/L)          | 2.07 (1.79-2.40)    | 1.4 × 10 <sup>-22</sup> | 0.031          | 0.89 (0.53-1.51)    | 6.8 × 10 <sup>-1</sup> | 0.045          |
| Increased alanine aminotransferase (U/L)            | 3.98 (3.39-4.68)    | 1.7 × 10 <sup>-63</sup> | 0.064          | -                   | -                      | -              |
| Increased apolipoprotein A-I (mg/L)                 | 0.55 (0.43-0.70)    | 1.8 × 10 <sup>-6</sup>  | 0.011          | 0.49 (0.29-0.85)    | 1.1 × 10 <sup>-2</sup> | 0.063          |
| Increased insulin sensitivity index                 | 0.29 (0.22-0.39)    | 8.3 × 10 <sup>-16</sup> | 0.087          | 0.18 (0.09-0.34)    | 9.8 × 10 <sup>-8</sup> | 0.120          |
| Increased insulin resistance index                  | 2.42 (1.81-3.22)    | 1.7 × 10 <sup>-9</sup>  | 0.034          | 4.52 (2.51-8.15)    | 5.3 × 10 <sup>-7</sup> | 0.106          |
| Decreased corrected insulin response                | 1.70 (1.18-2.45)    | 4.5 × 10 <sup>-3</sup>  | 0.028          | 2.33 (1.22-4.46)    | 1.0 × 10 <sup>-2</sup> | 0.080          |
| Decreased disposition index                         | 4.91 (3.29-7.33)    | 7.6 × 10 <sup>-15</sup> | 0.151          | 39.41 (9.56-162.40) | 3.7 × 10 <sup>-7</sup> | 0.216          |

Nagelkerke R-square (R<sup>2</sup>) is for the full model, denotes percent of type 2 diabetes risk explained by risk factors. The odds ratios for risk of developing type 2 diabetes and R<sup>2</sup> and are calculated using logistic regression analyses adjusted for age at participation and sex.

**Supplementary Table 2D. Comparison of baseline clinical factors predicting type 2 diabetes in Malmö and Botnia prospective studies between subjects from the highest and lowest quartiles (univariate regression analysis): adjusted for body mass index.**

|   | Malmö               |                         |                | Botnia              |                        |                |
|---|---------------------|-------------------------|----------------|---------------------|------------------------|----------------|
|   | Odds ratio (95% CI) | P value                 | R <sup>2</sup> | Odds ratio (95% CI) | P value                | R <sup>2</sup> |
| Increased body mass index (kg/height <sup>2</sup> ) | 4.94 (4.22-5.79)    | 8.2 × 10 <sup>-88</sup> | 0.079          | 9.29 (3.83-22.56)   | 8.5 × 10 <sup>-7</sup> | 0.132          |
| Increased waist (cm)                                | -                   | -                       | -              | 5.99 (1.71-20.99)   | 5.2 × 10 <sup>-3</sup> | 0.168          |
| Increased blood pressure (mmHg)                     |                     |                         |                |                     |                        |                |
| Systolic  | 1.63 (1.40-1.90)    | 2.8 × 10 <sup>-10</sup> | 0.069          | 3.14 (1.40-7.04)    | 5.4 × 10 <sup>-3</sup> | 0.136          |
| Diastolic   | 1.57 (1.37-1.81)    | 3.1 × 10 <sup>-10</sup> | 0.070          | 1.50 (0.82-2.75)    | 1.9 × 10 <sup>-1</sup> | 0.121          |
| Increased triglycerides (mmol/L)                    | 2.88 (2.44-3.41)    | 4.6 × 10 <sup>-35</sup> | 0.096          | 1.85 (0.99-3.45)    | 5.3 × 10 <sup>-2</sup> | 0.109          |
| Increased γ-glutamyltransferase (U/L)               | 2.31 (1.92-2.78)    | 5.8 × 10 <sup>-19</sup> | 0.092          | 2.36 (1.18-4.74)    | 1.6 × 10 <sup>-2</sup> | 0.122          |
| Increased aspartate aminotransferase (U/L)          | 1.63 (1.40-1.90)    | 2.4 × 10 <sup>-10</sup> | 0.068          | 0.73 (0.42-1.26)    | 2.6 × 10 <sup>-1</sup> | 0.114          |
| Increased alanine aminotransferase (U/L)            | 2.52 (2.12-3.00)    | 8.5 × 10 <sup>-26</sup> | 0.099          | -                   | -                      | -              |
| Increased apolipoprotein A-I (mg/L)                 | 0.59 (0.46-0.76)    | 4.3 × 10 <sup>-5</sup>  | 0.053          | 0.62 (0.36-1.08)    | 9.2 × 10 <sup>-2</sup> | 0.099          |
| Increased insulin sensitivity index                 | 0.42 (0.30-0.58)    | 1.3 × 10 <sup>-7</sup>  | 0.127          | 0.31 (0.16-0.61)    | 6.3 × 10 <sup>-4</sup> | 0.156          |
| Increased insulin resistance index                  | 1.76 (1.30-2.39)    | 2.7 × 10 <sup>-4</sup>  | 0.065          | 2.48 (1.33-4.63)    | 4.4 × 10 <sup>-3</sup> | 0.150          |
| Decreased corrected insulin response                | 2.31 (1.56-3.42)    | 2.9 × 10 <sup>-5</sup>  | 0.109          | 2.69 (1.46-4.97)    | 1.5 × 10 <sup>-3</sup> | 0.148          |
| Decreased disposition index                         | 4.10 (2.72-6.18)    | 1.7 × 10 <sup>-11</sup> | 0.202          | 26.50 (6.42-109.43) | 5.9 × 10 <sup>-6</sup> | 0.259          |

Nagelkerke R-square (R<sup>2</sup>) is for the full model, denotes percent of type 2 diabetes risk explained by risk factors. The odds ratios for risk of developing type 2 diabetes and R<sup>2</sup> and are calculated using logistic regression analyses adjusted for age at participation, body mass index, and sex.

**Supplementary Table 2E. Comparison of baseline clinical factors predicting progression from normal glucose tolerance or from impaired fasting glucose or impaired glucose tolerance to type 2 diabetes in the Malmö study between individuals from the highest and lowest quartiles (univariate regression analysis): adjusted for body mass index.**

|   | From normal glucose tolerance to type 2 diabetes |                         |                | From impaired fasting glucose or impaired glucose tolerance to type 2 diabetes |                         |                |
|---|--|-------------------------|----------------|--|-------------------------|----------------|
|   | Odds ratio (95% CI)                              | P value                 | R <sup>2</sup> | Odds ratio (95% CI)  | P value                 | R <sup>2</sup> |
| Increased body mass index (kg/height <sup>2</sup> ) | 4.76 (3.89-5.83)                                 | 2.6 × 10 <sup>-51</sup> | 0.064          | 4.20 (3.27-5.41)   | 4.4 × 10 <sup>-29</sup> | 0.114          |
| Increased blood pressure (mmHg)                     |  |                         |                |  |                         |                |
| Systolic  | 1.35 (1.13-1.62)                                 | 9.2 × 10 <sup>-4</sup>  | 0.053          | 1.59 (1.23-2.06)   | 4.3 × 10 <sup>-4</sup>  | 0.084          |
| Diastolic   | 1.49 (1.20-1.83)                                 | 2.4 × 10 <sup>-4</sup>  | 0.057          | 1.59 (1.25-2.02)   | 1.3 × 10 <sup>-4</sup>  | 0.110          |
| Increased triglycerides (mmol/L)                    | 2.67 (2.15-3.31)                                 | 5.5 × 10 <sup>-19</sup> | 0.076          | 2.59 (1.96-3.43)   | 2.7 × 10 <sup>-11</sup> | 0.127          |
| Increased γ-glutamyltransferase (U/L)               | 2.08 (1.66-2.61)                                 | 2.5 × 10 <sup>-10</sup> | 0.071          | 2.63 (1.93-3.58)   | 8.3 × 10 <sup>-10</sup> | 0.138          |
| Increased aspartate aminotransferase (U/L)          | 1.52 (1.25-1.85)                                 | 2.3 × 10 <sup>-5</sup>  | 0.050          | 1.69 (1.31-2.18)   | 6.5 × 10 <sup>-5</sup>  | 0.111          |
| Increased alanine aminotransferase (U/L)            | 2.28 (1.84-2.82)                                 | 3.6 × 10 <sup>-14</sup> | 0.070          | 2.68 (2.03-3.52)   | 2.2 × 10 <sup>-12</sup> | 0.135          |
| Increased apolipoprotein A-I (mg/L)                 | 0.53 (0.38-0.74)                                 | 1.9 × 10 <sup>-4</sup>  | 0.095          | 0.58 (0.39-0.87)   | 8.8 × 10 <sup>-3</sup>  | 0.075          |
| Increased insulin sensitivity index                 | 0.52 (0.34-0.79)                                 | 2.1 × 10 <sup>-3</sup>  | 0.083          | 0.42 (0.24-0.73)   | 1.9 × 10 <sup>-3</sup>  | 0.158          |
| Increased insulin resistance index                  | 1.63 (1.12-2.37)                                 | 1.1 × 10 <sup>-2</sup>  | 0.102          | 2.03 (1.21-3.40)   | 7.6 × 10 <sup>-3</sup>  | 0.141          |
| Decreased corrected insulin response                | 2.11 (1.30-3.41)                                 | 2.5 × 10 <sup>-3</sup>  | 0.101          | 1.90 (0.94-3.83)   | 7.4 × 10 <sup>-2</sup>  | 0.133          |
| Decreased disposition index                         | 3.30 (2.02-5.38)                                 | 1.7 × 10 <sup>-6</sup>  | 0.168          | 3.56 (1.78-7.12)   | 3.3 × 10 <sup>-4</sup>  | 0.267          |

Nagelkerke R-square (R<sup>2</sup>) is for the full model, denotes percent of type 2 diabetes risk explained by risk factors. The odds ratios for risk of developing type 2 diabetes and R<sup>2</sup> and are calculated using logistic regression analyses adjusted for age at inclusion, body mass index and sex.

**Supplementary Table 3. Genetic factors predicting type 2 diabetes in subjects with normal glucose tolerance or with impaired fasting glucose or impaired glucose tolerance at baseline in the Malmö prospective study.**

|     |   |    | Normal glucose tolerance |        |                     |                      |                                  |                      | Impaired fasting glucose or impaired glucose tolerance |        |                     |                      |                                  |                      |                  |
|-----|---|----|--------------------------|--------|---------------------|----------------------|----------------------------------|----------------------|--|--------|---------------------|----------------------|----------------------------------|----------------------|------------------|
|     |   |    | Primary model            |        |                     | Alternative model    |                                  |                      | Primary model  |        |                     | Alternative model    |                                  |                      |                  |
| Chr | Gene SNP                                | RA | RA <sub>AFF</sub>        | Number | Odds ratio (95% CI) | P value              | Odds ratio (95% CI)              | P value              | RA <sub>AFF</sub>                                      | Number | Odds ratio (95% CI) | P value              | Odds ratio (95% CI)              | P value              | P <sub>het</sub> |
| 10  | <i>TCF7L2</i><br>rs7903146              | T  | 0.30                     | 12015  | 1.27<br>(1.16-1.40) | $2.7 \times 10^{-7}$ | Dominant<br>1.38<br>(1.23-1.56)  | $9.8 \times 10^{-8}$ | 0.32   | 3800   | 1.30<br>(1.15-1.47) | $2.7 \times 10^{-5}$ | Dominant<br>1.40<br>(1.19-1.64)  | $3.4 \times 10^{-5}$ | 0.62             |
| 3   | <i>PPARG</i><br>rs1801282               | C  | 0.87                     | 12155  | 1.15<br>(1.01-1.30) | $3.0 \times 10^{-2}$ | -                                | -                    | 0.88   | 3838   | 1.29<br>(1.09-1.53) | $3.6 \times 10^{-3}$ | -                                | -                    | 0.25             |
| 16  | <i>FTO</i><br>rs9939609                 | A  | 0.44                     | 12117  | 1.16<br>(1.06-1.26) | $7.2 \times 10^{-4}$ | Recessive<br>1.30<br>(1.12-1.51) | $4.4 \times 10^{-4}$ | 0.43   | 3814   | 1.13<br>(1.01-1.27) | $2.8 \times 10^{-2}$ | Recessive<br>1.20<br>(0.98-1.47) | $8.0 \times 10^{-2}$ | 0.57             |
| 11  | <i>KCNJ11</i><br>rs5219                 | T  | 0.40                     | 11779  | 1.11<br>(1.02-1.21) | $1.4 \times 10^{-2}$ | -                                | -                    | 0.42   | 3821   | 1.15<br>(1.02-1.29) | $1.9 \times 10^{-2}$ | -                                | -                    | 0.74             |
| 1   | <i>NOTCH2</i><br>rs10923931             | T  | 0.10                     | 11878  | 1.08<br>(0.94-1.24) | $2.7 \times 10^{-1}$ | -                                | -                    | 0.12   | 3711   | 1.15<br>(0.97-1.38) | $1.1 \times 10^{-1}$ | -                                | -                    | 0.49             |
| 4   | <i>WFS1</i><br>rs10010131               | G  | 0.60                     | 12121  | 1.13<br>(1.04-1.23) | $3.6 \times 10^{-3}$ | Recessive<br>1.23<br>(1.09-1.39) | $8.0 \times 10^{-4}$ | 0.59   | 3823   | 1.07<br>(0.95-1.20) | $2.4 \times 10^{-1}$ | Recessive<br>1.08<br>(0.91-1.28) | $3.8 \times 10^{-1}$ | 0.48             |
| 6   | <i>CDKAL1</i><br>rs7754840              | C  | 0.33                     | 11750  | 1.09<br>(0.99-1.19) | $7.0 \times 10^{-2}$ | Recessive<br>1.21<br>(1.00-1.46) | $5.0 \times 10^{-2}$ | 0.34   | 3737   | 1.12<br>(0.99-1.26) | $6.0 \times 10^{-2}$ | Recessive<br>1.18<br>(0.93-1.50) | $1.8 \times 10^{-1}$ | 0.68             |
| 3   | <i>IGF2BP2</i><br>rs4402960             | A  | 0.32                     | 11641  | 1.12<br>(1.03-1.23) | $1.1 \times 10^{-2}$ | Recessive<br>1.23<br>(1.01-1.49) | $4.1 \times 10^{-2}$ | 0.32   | 3516   | 1.02<br>(0.90-1.15) | $8.1 \times 10^{-1}$ | Recessive<br>1.19<br>(0.91-1.54) | $2.0 \times 10^{-1}$ | 0.20             |
| 8   | <i>SLC30A8</i><br>rs13266634            | C  | 0.70                     | 12109  | 1.11<br>(1.01-1.21) | $2.5 \times 10^{-2}$ | -                                | -                    | 0.70   | 3822   | 1.08<br>(0.95-1.21) | $2.3 \times 10^{-1}$ | -                                | -                    | 0.66             |
| 7   | <i>JAZF1</i><br>rs864745                | A  | 0.52                     | 12119  | 1.06<br>(0.97-1.15) | $1.7 \times 10^{-1}$ | -                                | -                    | 0.54   | 3825   | 1.09<br>(0.98-1.22) | $1.2 \times 10^{-1}$ | -                                | -                    | 0.64             |
| 10  | <i>HHEX</i><br>rs1111875                | G  | 0.60                     | 12127  | 1.06<br>(0.97-1.15) | $1.9 \times 10^{-1}$ | -                                | -                    | 0.61   | 3815   | 1.06<br>(0.95-1.19) | $3.1 \times 10^{-1}$ | -                                | -                    | 0.90             |
| 2   | <i>THADA</i><br>rs7578597               | T  | 0.90                     | 11894  | 1.12<br>(0.97-1.30) | $1.1 \times 10^{-1}$ | -                                | -                    | 0.90   | 3726   | 1.05<br>(0.66-1.27) | $6.0 \times 10^{-1}$ | -                                | -                    | 0.73             |
| 9   | <i>CDKN2A</i><br>rs10811661             | T  | 0.85                     | 11460  | 1.10<br>(0.98-1.24) | $1.0 \times 10^{-1}$ | -                                | -                    | 0.85   | 3672   | 1.04<br>(0.89-1.22) | $5.9 \times 10^{-1}$ | -                                | -                    | 0.53             |
| 12  | <i>TSPAN8/<br/>LGR5</i><br>rs7961581    | G  | 0.26                     | 11883  | 1.02<br>(0.93-1.13) | $6.3 \times 10^{-1}$ | -                                | -                    | 0.27   | 3711   | 1.05<br>(0.93-1.19) | $4.3 \times 10^{-1}$ | -                                | -                    | 0.69             |
| 3   | <i>ADAMTS9</i><br>rs4607103             | C  | 0.78                     | 11959  | 1.05<br>(0.95-1.16) | $3.4 \times 10^{-1}$ | -                                | -                    | 0.77   | 3770   | 1.04<br>(0.91-1.19) | $5.4 \times 10^{-1}$ | -                                | -                    | 0.92             |
| 10  | <i>CDC123/<br/>CAMK1D</i><br>rs12779790 | G  | 0.19                     | 11849  | 1.03<br>(0.93-1.15) | $5.4 \times 10^{-1}$ | -                                | -                    | 0.19   | 3698   | 0.97<br>(0.84-1.12) | $6.5 \times 10^{-1}$ | -                                | -                    | 0.49             |

RA denotes risk allele in the Malmö and Botnia studies. The primary genetic models are additive; alternative models are indicated. The odds ratios for risk of developing type 2 diabetes are calculated using logistic regression analyses adjusted for age at participation and sex. P<sub>het</sub> = P value from the Breslow-Day for between-studies heterogeneity.

| Supplementary Table 4. Area under the ROC curves (C Statistics) for different models predicting type 2 diabetes. |             |        |       |                                 |        |        |                                 |
|--|-------------|--------|-------|---------------------------------|--------|--------|---------------------------------|
|  |             | Malmö  |       |                                 | Botnia |        |                                 |
|  |             | Number | AUC   | H-L chi <sup>2</sup><br>P value | Number | AUC    | H-L chi <sup>2</sup><br>P value |
| <b>Model I:</b> personal (Wilson et al)  | Categorical | 13,005 | 0.692 | 0.38                            | 2,730  | 0.736  | 0.08                            |
|  | Continuous  | 13,005 | 0.707 | 0.23                            | 2,730  | 0.769  | 0.03                            |
| <b>Model II:</b> clinical (Wilson et al)   | Categorical | 13,005 | 0.729 | 0.91                            | 2,730  | 0.755  | 0.11                            |
|  | Continuous  | 13,005 | 0.743 | 0.08                            | 2,730  | 0.786  | 0.13                            |
| <b>Model III:</b> clinical (insulin secretion)   | Continuous  | 1583   | 0.719 | 0.11                            | 2,487  | 0.838  | 0.37                            |
| <b>Model II+III</b>  | Continuous  | 1583   | 0.737 | 0.23                            | 2,302  | 0.832  | 0.42                            |
| <b>Model IV:</b> genetic   | -           | 10,600 | 0.626 | 0.63                            | 1,907  | 0.6821 | 0.08                            |
| <b>Model I+IV</b>  | Continuous  | 10,600 | 0.721 | 0.71                            | -      | -      | -                               |
| <b>Model II+IV</b>   | Continuous  | 10,600 | 0.753 | 0.50                            | 1737   | 0.8014 | 0.43                            |
| <b>Model III+IV</b>  | Continuous  | 1203   | 0.735 | 0.36                            | -      | -      | -                               |
| <b>Model II+III+IV</b>   | Continuous  | 1203   | 0.749 | 0.31                            | -      | -      | -                               |

Personal (age, sex, family history of diabetes, body mass index) and clinical (age, sex, family history of diabetes, body mass index, blood pressure, HDL cholesterol (available only in Botnia), triglycerides, waist circumference (available only in Botnia), fasting plasma glucose) models (Wilson et al).

Disposition index was used as a measure of insulin secretion. HL = Hosmer-Lemeshow chi<sup>2</sup>.

Model III – we replaced the clinical variables suggested by Wilson et al. by measures of insulin secretion.

Comparisons:

Model I+IV vs Model I: P<0.0001.

Model II+IV vs Model II: MPP, P=0.0001; Botnia, P=0.23.

Model III+IV vs Model III: P<0.05.

Model II+III+IV vs Model II+III: P<0.05.

Model II+III vs Model II: MPP, P=0.001; Botnia, P=0.006.

Model III vs Model I: P=0.0002.

| <b>Supplementary Table 5. Comparison of predicted risks of type 2 diabetes with and without genetic risk factors using reclassification approach.</b> |   |                      |               |                       |                  |                      |               |                       |
|---|---|----------------------|---------------|-----------------------|------------------|----------------------|---------------|-----------------------|
| Diabetes risk category<br>Clinical factors  | Change in classification after adding genetic to clinical factors |                      |               |                       |                  |                      |               |                       |
|   | Malmö   |                      |               |                       | Botnia           |                      |               |                       |
|   | 0 to10%<br>N (%)  | >10 to ≤20%<br>N (%) | >20%<br>N (%) | Reclassified<br>N (%) | 0 to10%<br>N (%) | >10 to ≤20%<br>N (%) | >20%<br>N (%) | Reclassified<br>N (%) |
| All participants  |   |                      |               |                       |                  |                      |               |                       |
| 0 to10% (N, MPP=4,859; Botnia=1,499)  | 4472 (92.0)   | 387 (8.0)            | 0 (0)         | 387 (8.0)             | 1435 (95.7)      | 64 (4.3)             | 0 (0.0)       | 64 (4.3)              |
| >10 to ≤20% (N, MPP=3,378; Botnia=176)  | 546 (16.2)  | 2458 (72.8)          | 374 (11.1)    | 920 (27.2)            | 60 (34.1)        | 94 (53.4)            | 22 (12.5)     | 82 (46.6)             |
| >20% (N, MPP=2,363; Botnia=62)  | 1 (0.0)   | 345 (14.6)           | 2017 (85.4)   | 346 (14.6)            | 0 (0.0)          | 18 (29.0)            | 44 (71.0)     | 44 (71.0)             |
| Subjects who developed type 2 diabetes  |   |                      |               |                       |                  |                      |               |                       |
| 0 to10% (N, MPP=278; Botnia=52)   | 236 (84.9)  | 42 (15.1)            | 0 (0.0)       | 42 (15.1)             | 42 (2.8)         | 10 (0.7)             | 0 (0.0)       | 10 (0.7)              |
| >10 to ≤20% (N, MPP=478; Botnia=22)   | 35 (7.3)  | 353 (73.8)           | 90 (18.8)     | 125 (26.2)            | 6 (3.4)          | 8 (4.5)              | 8 (4.5)       | 14 (63.6)             |
| >20% (N, MPP=757; Botnia=17)  | 1 (0.1)   | 56 (7.4)             | 700 (92.5)    | 57 (7.5)              | 0 (0.0)          | 4 (6.5)              | 13 (21.0)     | 4 (6.5)               |
| Subjects who did not develop type 2 diabetes  |   |                      |               |                       |                  |                      |               |                       |
| 0 to10% (N, MPP=4,581, Botnia=1,447)  | 4236 (92.5)   | 345 (7.5)            | 0 (0.0)       | 345 (7.5)             | 1393 (92.9)      | 54 (3.6)             | 0 (0.0)       | 54 (3.6)              |
| >10 to ≤20% (N, MPP=2,900; Botnia=154)  | 511 (17.6)  | 2105 (72.6)          | 284 (9.8)     | 795 (27.4)            | 54 (30.7)        | 86 (48.9)            | 14 (8.0)      | 68 (44.2)             |
| >20% (N, MPP=1,606; Botnia=45)  | 0 (0.0)   | 289 (18.0)           | 1317 (82.0)   | 289 (18.0)            | 0 (0.0)          | 14 (22.6)            | 31 (50.0)     | 14 (22.6)             |

Comparison is for clinical model with and without genetic risk factors (11 SNPs).

The numbers (%) in rows refer to the number of individuals in the category before re-classification.

The numbers (%) in columns refer to the number of individuals who remained in the category after re-classification.

| <b>Supplementary Table 6. Area under the ROC curves (C Statistics) for different models predicting type 2 diabetes in quintiles of duration of follow-up.</b> |                               |                            |                 |                 |                          |
|---|-------------------------------|----------------------------|-----------------|-----------------|--------------------------|
| <b>Quintile</b>   | <b>Number, converters (%)</b> | <b>Follow-up (mean±SD)</b> | <b>Clinical</b> | <b>Genetic</b>  | <b>Clinical +Genetic</b> |
| <b>I</b>  | 155 (7.3)                     | 16.3 (2.5)                 | 0.754 (0.00061) | 0.565 (0.00057) | 0.755 (0.00062)          |
| <b>II</b>   | 281 (13.3)                    | 21.4 (1.1)                 | 0.775 (0.00045) | 0.622 (0.00031) | 0.791 (0.00039)          |
| <b>III</b>  | 355 (16.7)                    | 23.7 (0.6)                 | 0.731 (0.00022) | 0.566 (0.00028) | 0.736 (0.00022)          |
| <b>IV</b>   | 381 (18.0)                    | 26.2 (1.0)                 | 0.705 (0.00028) | 0.599 (0.00025) | 0.713 (0.00028)          |
| <b>V</b>  | 341 (16.1)                    | 28.4 (0.5)                 | 0.674 (0.00046) | 0.623 (0.00027) | 0.688 (0.00046)          |

Data are AUC (variance). Genetic model was adjusted for age at participation and sex. Clinical model was calculated as described by Wilson et al.

Genetic I versus V: P=0.01. Clinical I versus V: P= 0.01.

## SUPPLEMENTARY FIGURES

**Supplementary Figure 1.** Frequency distribution of risk alleles in the Malmö and Botnia studies.

**Supplementary Figure 2.** Risk of type 2 diabetes in relation to waist circumference or waist-to-hip ratio and family history of diabetes or genetic risk factors.

**Supplementary Figure 3.** Individual effect of studied genetic variants on changes in body mass index, insulin sensitivity (ISI), insulin secretion measured as corrected incremental insulin response during OGTT (CIR) or as disposition index, i.e. insulin secretion adjusted for insulin sensitivity (DI) over time in non-diabetic individuals from the Botnia prospective study.

**Supplementary Figure 4.** Area under the ROC curves (C Statistics) for different models predicting type 2 diabetes in the Malmö study.

**Supplementary Figure 5.** Risk of type 2 diabetes, and changes in diabetes-related phenotypes over time in non-diabetic individuals from the Malmö and the Botnia prospective study in relation to genetic risk score excluding the FTO variant.

## FIGURE LEGENDS

**Supplementary Figure 1.** Frequency distribution of risk alleles in the Malmö and Botnia studies.

Based upon the frequency distribution of risk alleles of the 11 SNPs, which significantly predicted type 2 diabetes, we defined a low and high genetic risk group as the quintile with the lowest and highest number of risk alleles; the corresponding cut-off values marked in bold were  $\leq 8 / \geq 12$  for both Malmö (3,346 (20.8%) / 3,123 (19.4%)) and Botnia cohorts (500 (20.5%) / 404 (16.5%)).

**Supplementary Figure 2.** Risk of type 2 diabetes in relation to waist circumference or waist-to-hip ratio and family history of diabetes or genetic risk factors.

We evaluated risk of incident type 2 diabetes in relation to quartiles of waist or waist-to-hip ratio (at follow up in MPP) and family history of diabetes or genetic risk score. A first-degree family history of type 2 diabetes doubled the risk of diabetes, which increased with increasing quartile of waist circumference (Panel A) or waist-to-hip ratio (Panel B). Panel C and D show a stepwise increase in diabetes risk with increasing number of risk alleles and increasing quartiles of waist circumference or waist-to-hip ratio.

**Supplementary Figure 3.** Individual effect of studied genetic variants on changes in body mass index, insulin sensitivity (ISI), insulin secretion measured as corrected incremental insulin response during OGTT (CIR) or as disposition index, i.e. insulin secretion adjusted for insulin sensitivity (DI) over time in non-diabetic individuals from the Botnia prospective study. Panel A: *TCF7L2* rs7903146, Panel B: *PPARG* rs1801282, Panel C: *FTO* rs9939609, Panel D: *KCNJ11* rs5219, Panel E: *NOTCH2* rs10923931, Panel F: *WFS1* rs10010131, Panel G: *CDKAL1* rs7754840, Panel H: *IGF2BP2* rs4402960, Panel I: *SLC30A8* rs13266634, Panel J: *JAZF1* rs864745, Panel K: *HHEX* rs1111875, Panel L: *THADA* Panel M: *CDKN2A/2B* rs10811661, Panel N: *TSPAN8/LGR5* rs7961581, Panel O: *ADAMTS9* rs4607103, Panel P: *CDC123/CAMK1D* rs12779790. The P values of genotype-phenotype correlations in non-diabetic participants from the Malmö and Botnia prospective studies are presented below. Genotype-phenotype correlations are analyzed under additive model (coded as 0,1,2), adjusted for age, sex, body mass index (when appropriate) and family dependence (in the Botnia study).

| Fig | Chr | Gene                 | SNP        | Malmö           |           | Botnia          |           |          |           |          |           |          |           |
|-----|-----|----------------------|------------|-----------------|-----------|-----------------|-----------|----------|-----------|----------|-----------|----------|-----------|
|     |     |                      |            | Body mass index |           | Body mass index |           | ISI      |           | CIR      |           | DI       |           |
|     |     |                      |            | Baseline        | Follow-up | Baseline        | Follow-up | Baseline | Follow-up | Baseline | Follow-up | Baseline | Follow-up |
| A   | 10  | <i>TCF7L2</i>        | rs7903146  | 0.64            | 0.53      | 0.49            | 0.90      | 0.90     | 0.32      | 0.022    | 0.14      | 0.029    | 0.47      |
| B   | 3   | <i>PPARG</i>         | rs1801282  | 0.11            | 0.11      | 0.02            | 0.02      | 0.74     | 0.33      | 0.0082   | 0.48      | 0.030    | 0.99      |
| C   | 16  | <i>FTO</i>           | rs9939609  | <0.0001         | <0.0001   | 0.04            | 0.01      | 0.83     | 0.48      | 0.51     | 0.31      | 0.56     | 0.17      |
| D   | 11  | <i>KCNJ11</i>        | rs5219     | 0.63            | 0.047     | 0.63            | 0.75      | 0.39     | 0.59      | 0.69     | 0.030     | 0.37     | 0.018     |
| F   | 1   | <i>NOTCH2</i>        | rs10923931 | 0.26            | 0.83      | 0.45            | 0.23      | 0.024    | 0.64      | 0.93     | 0.75      | 0.11     | 0.62      |
| G   | 4   | <i>WFS1</i>          | rs10010131 | 0.34            | 0.69      | 0.98            | 0.59      | 0.93     | 0.15      | 0.18     | 0.0027    | 0.21     | 0.078     |
| H   | 6   | <i>CDKAL1</i>        | rs7754840  | 0.09            | 0.06      | 0.44            | 0.34      | 0.20     | 0.26      | 0.075    | 0.00078   | 0.47     | 0.014     |
| I   | 3   | <i>IGF2BP2</i>       | rs4402960  | 0.98            | 0.28      | 0.60            | 0.93      | 0.12     | 0.32      | 0.10     | 0.068     | 0.011    | 0.013     |
| J   | 8   | <i>SLC30A8</i>       | rs13266634 | 0.37            | 0.88      | 0.37            | 0.84      | 0.53     | 0.66      | 0.0013   | 0.00021   | 0.0061   | 0.0012    |
| K   | 7   | <i>JAZF1</i>         | rs864745   | 0.052           | 0.003     | 0.94            | 0.96      | 0.81     | 0.52      | 0.53     | 0.33      | 0.35     | 0.19      |
| L   | 10  | <i>HHEX</i>          | rs1111875  | 0.77            | 0.21      | 0.36            | 0.28      | 0.78     | 0.53      | 0.087    | 0.00050   | 0.14     | 0.0093    |
| N   | 2   | <i>THADA</i>         | rs7578597  | 0.42            | 0.41      | 0.74            | 0.81      | 0.093    | 0.63      | 0.21     | 0.72      | 0.031    | 0.47      |
| M   | 9   | <i>CDKN2A</i>        | rs10811661 | 0.88            | 0.67      | 0.95            | 0.41      | 0.96     | 0.75      | 0.027    | 0.0058    | 0.040    | 0.016     |
| N   | 12  | <i>TSPAN8/LGR5</i>   | rs7961581  | 0.09            | 0.24      | 0.58            | 0.43      | 0.13     | 0.62      | 0.94     | 0.79      | 0.58     | 0.67      |
| O   | 3   | <i>ADAMTS9</i>       | rs4607103  | 0.02            | 0.004     | 0.48            | 0.68      | 0.97     | 0.13      | 0.83     | 0.037     | 0.79     | 0.87      |
| P   | 10  | <i>CDC123/CAMK1D</i> | rs12779790 | 0.06            | 0.06      | 0.25            | 0.12      | 0.12     | 0.68      | 0.77     | 0.18      | 0.19     | 0.24      |

**Supplementary Figure 4.** Area under the ROC curves (C Statistics) for different models predicting type 2 diabetes in the Malmö study

Panel A: Clinical model (age, sex, family history of diabetes, body mass index, blood pressure, triglycerides, fasting plasma glucose) *versus* clinical plus genetic risk factors (11 SNPs).

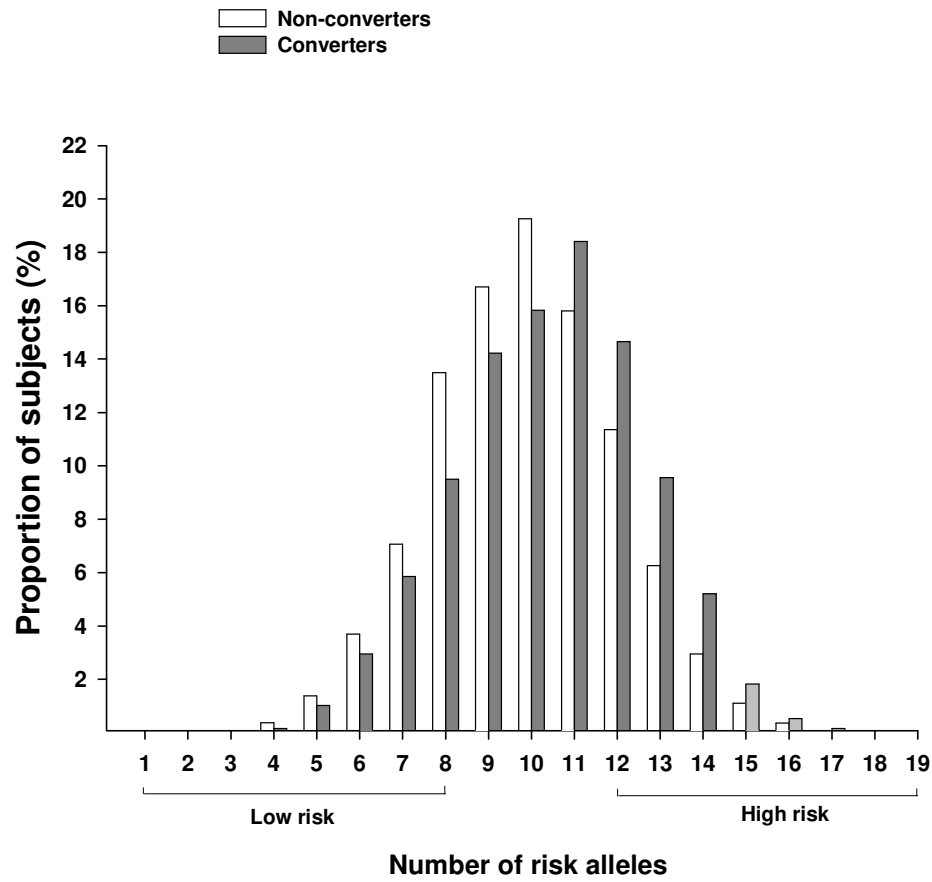
Panel B: personal (age, sex, family history of diabetes, body mass index) with insulin secretion (DI=disposition index) *versus* personal with insulin secretion plus genetic risk factors (11 SNPs).

**Supplementary Figure 5.** Risk of type 2 diabetes, and changes in diabetes-related phenotypes over time in non-diabetic individuals from the Malmö and the Botnia prospective study in relation to genetic risk score excluding the *FTO* variant.

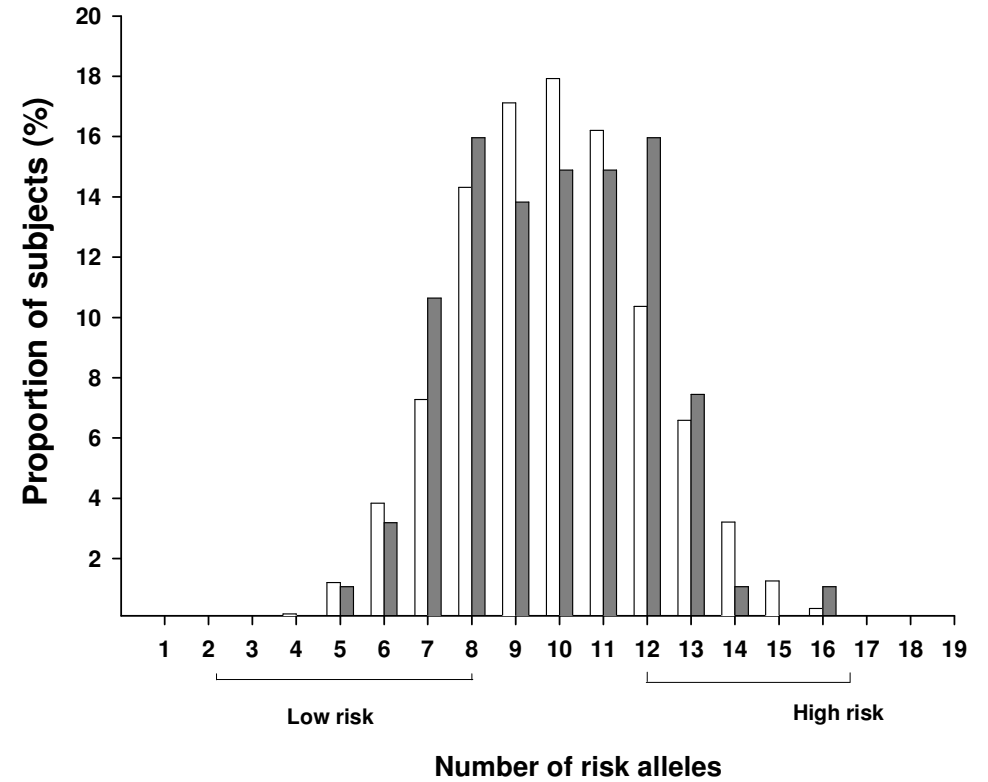
We evaluated the combined genetic effect of the risk alleles excluding *FTO* rs9939609 from the analysis of the genetic risk score as effect of *FTO* on BMI could to some extent bias the results if the increase in BMI over time was mostly driven by the risk genotype in *FTO*. Panel A shows incidence of type 2 diabetes in carriers of increasing number of risk alleles in 10 genes, which individually predicted future type 2 diabetes, in relation to quartiles of body mass index and Panel B in relation to low beta-cell function (disposition index) in the Malmö study; in the Botnia study: Panel C shows a similar increase in body mass index in carriers of high (in red) and low genetic risk (in blue); Panel D shows a similar worsening of insulin sensitivity in carriers of high and low genetic risk; Panel E shows an increase in corrected insulin secretion (CIR) over time which was smaller in carriers of low than high genetic risk; Panel F shows that the carriers of high genetic risk were unable to increase their beta-cell function (disposition index) to compensate for the increase in insulin resistance as effectively as carriers of low genetic risk. These figures demonstrate that excluding *FTO* from the genetic risk score did not change the results.

# Supplementary Figure 1

## A Malmoe

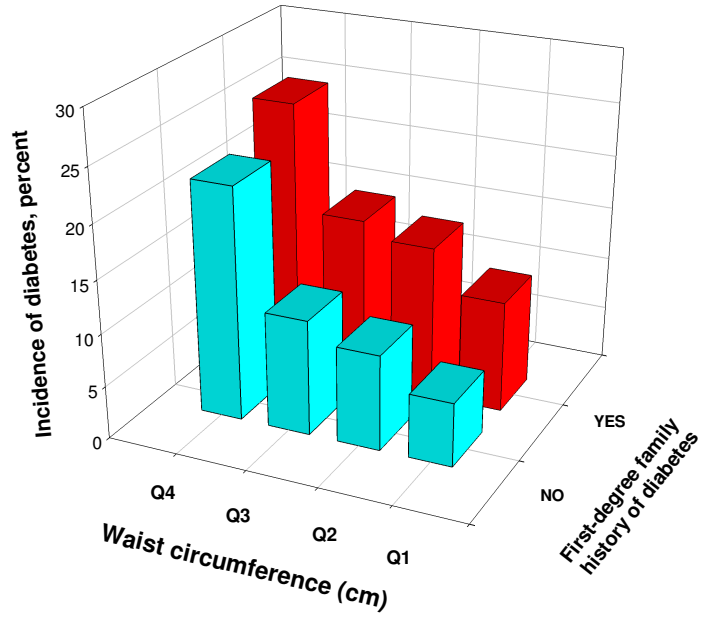


## B Botnia

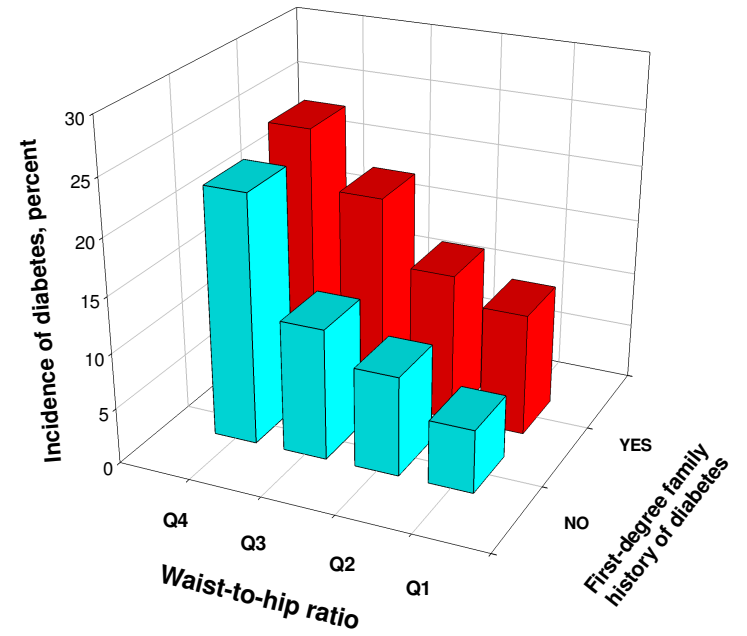


# Supplementary Figure 2

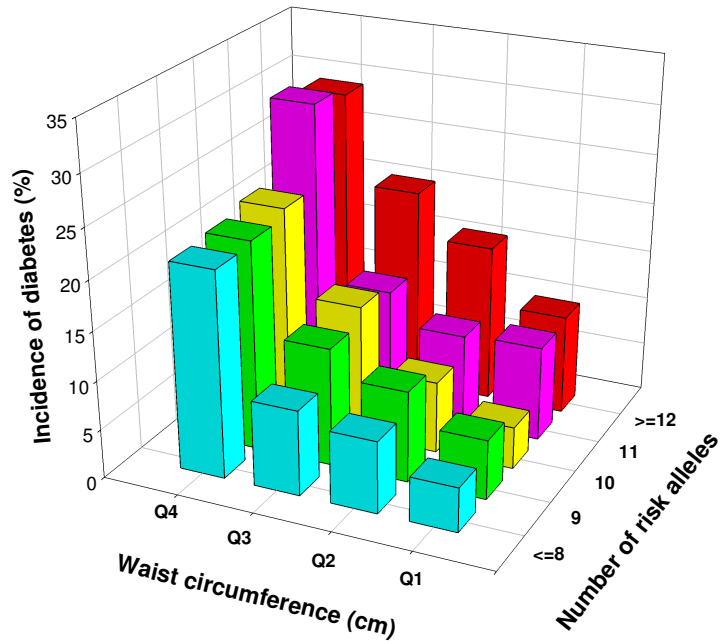
**A**



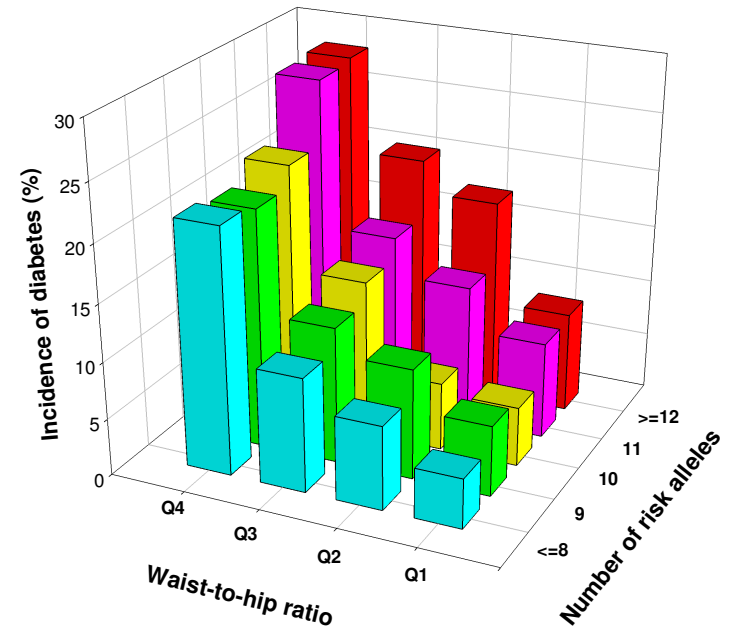
**B**



**C**

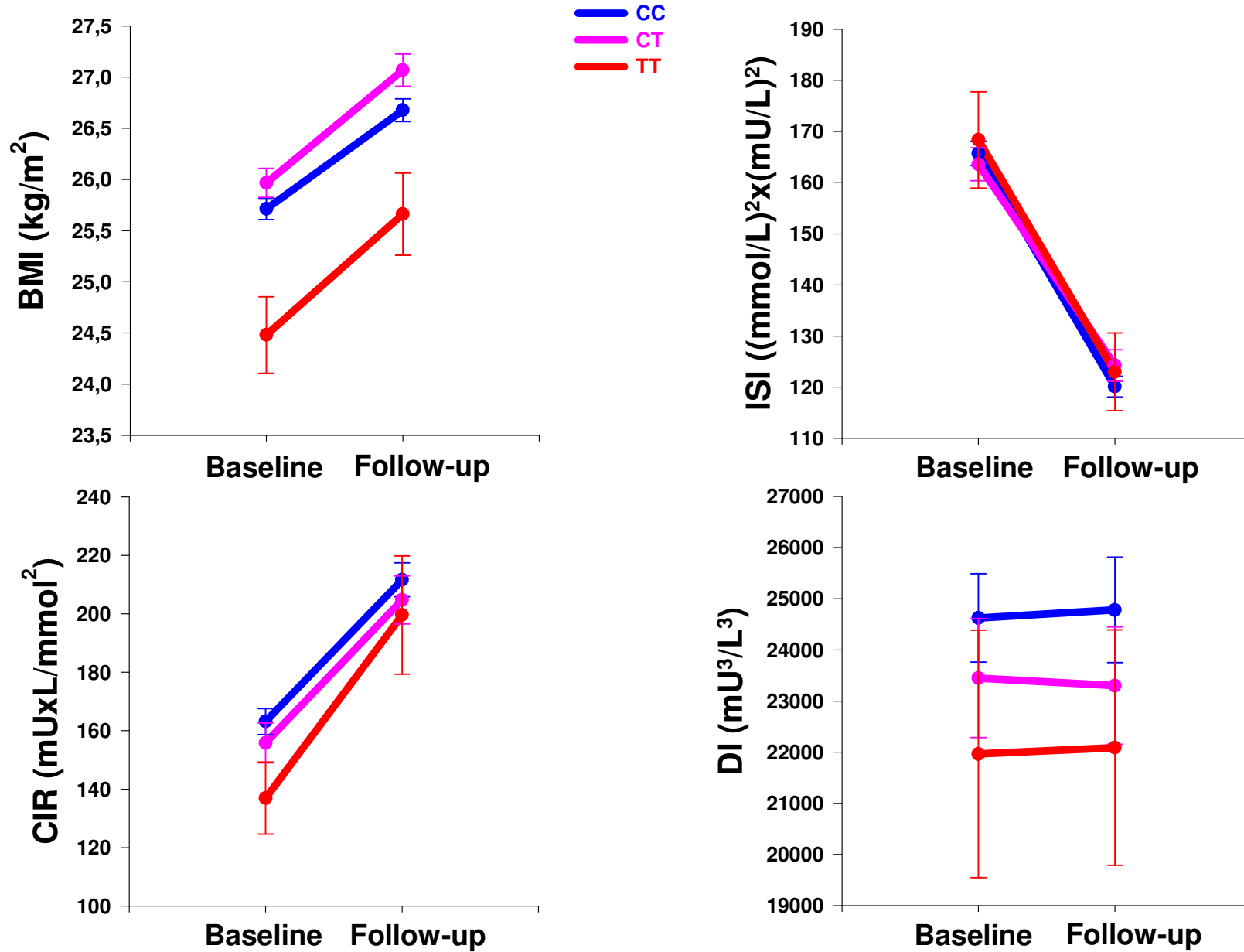


**D**



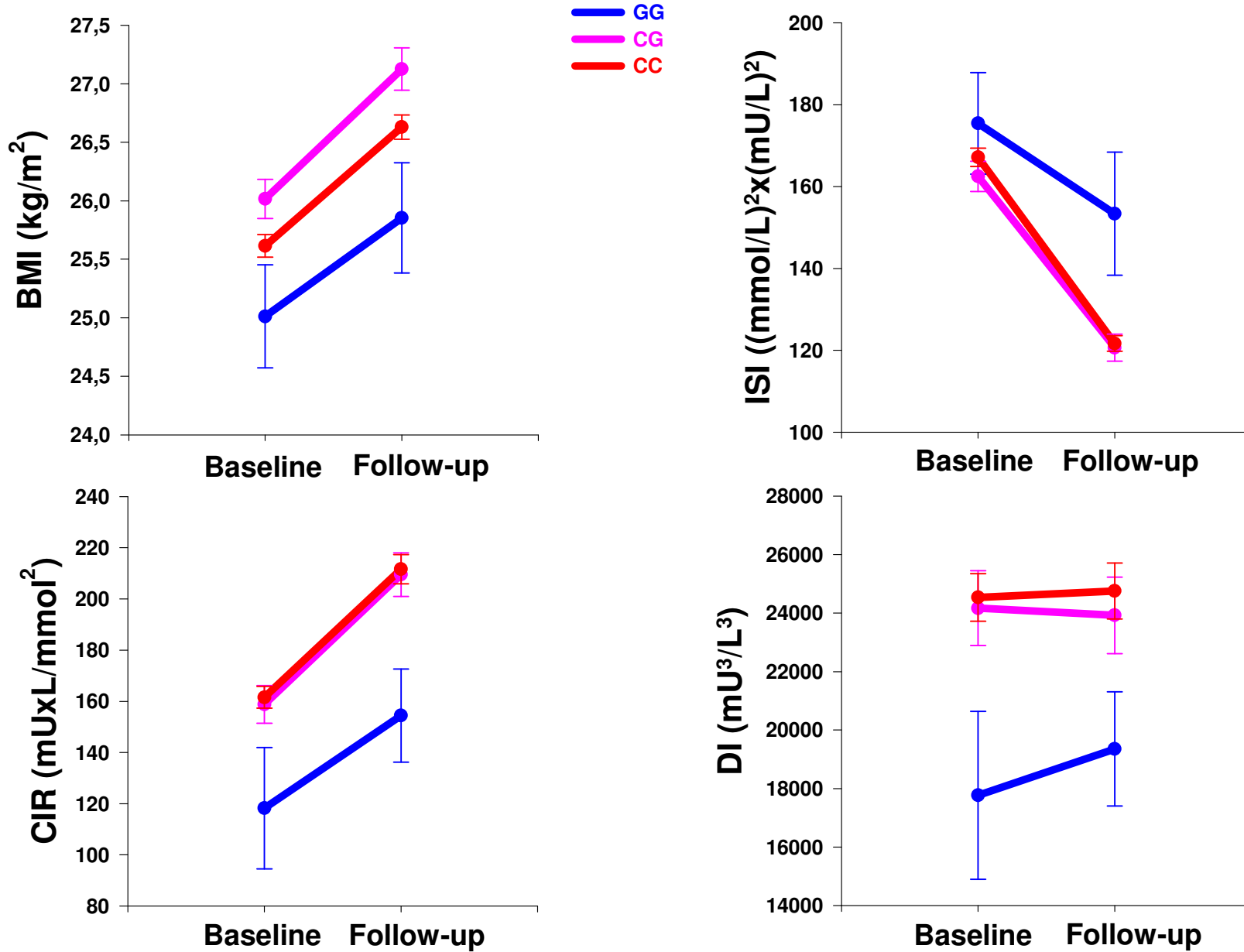
# Supplementary Figure 3

## A *TCF7L2* rs7903146



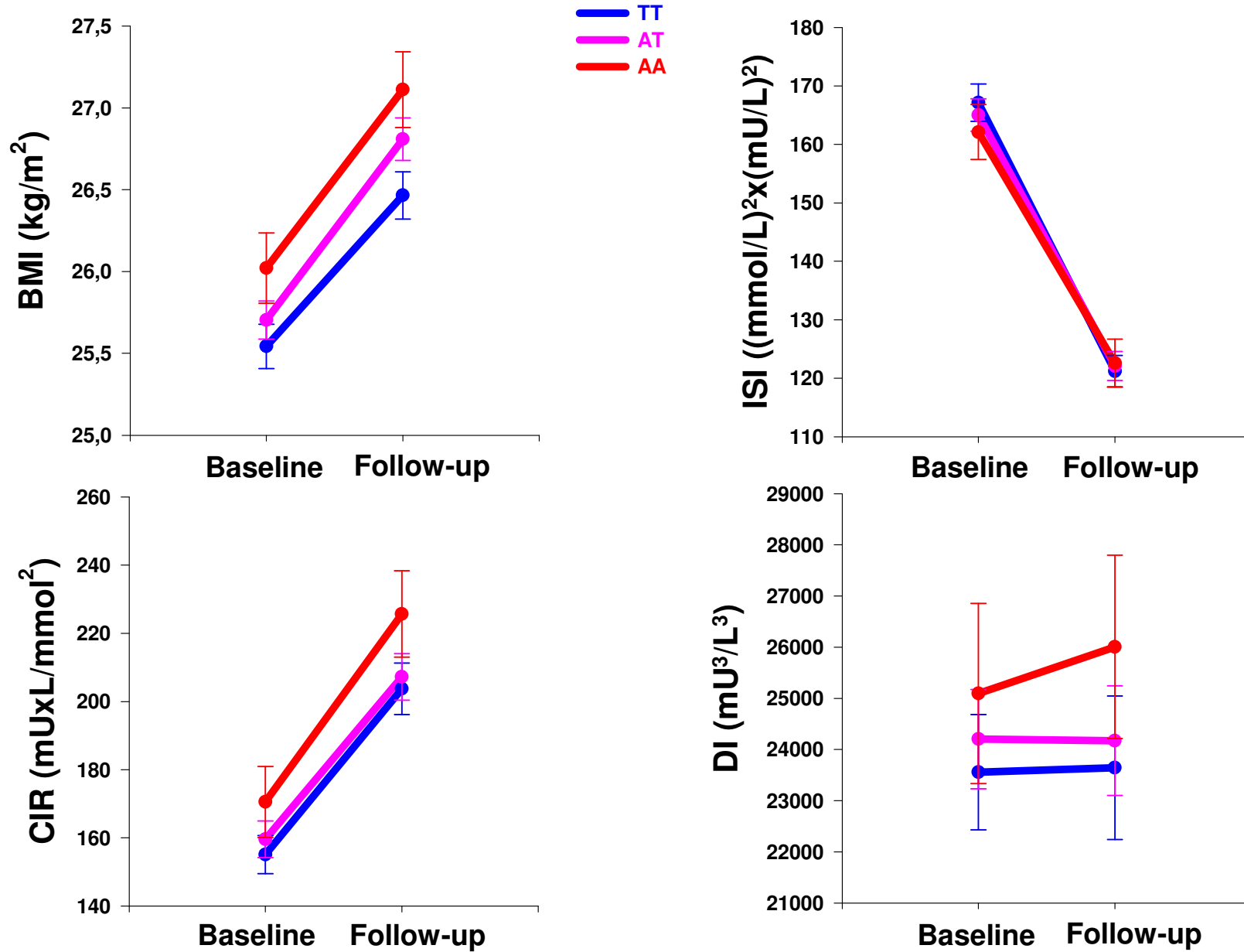
# Supplementary Figure 3

## B *PPARG* rs1801282



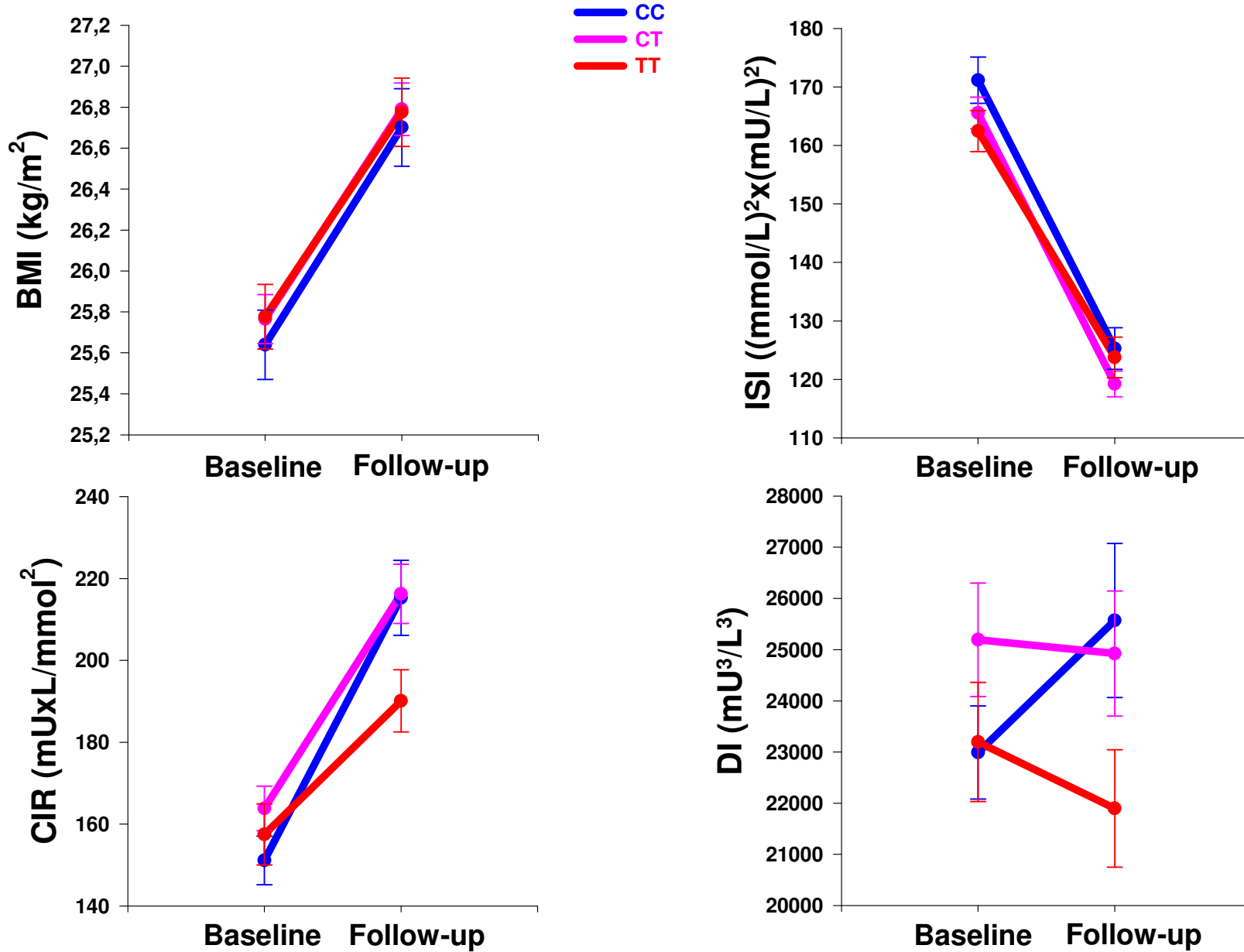
Supplementary Figure 3

C *FTO* rs9939609



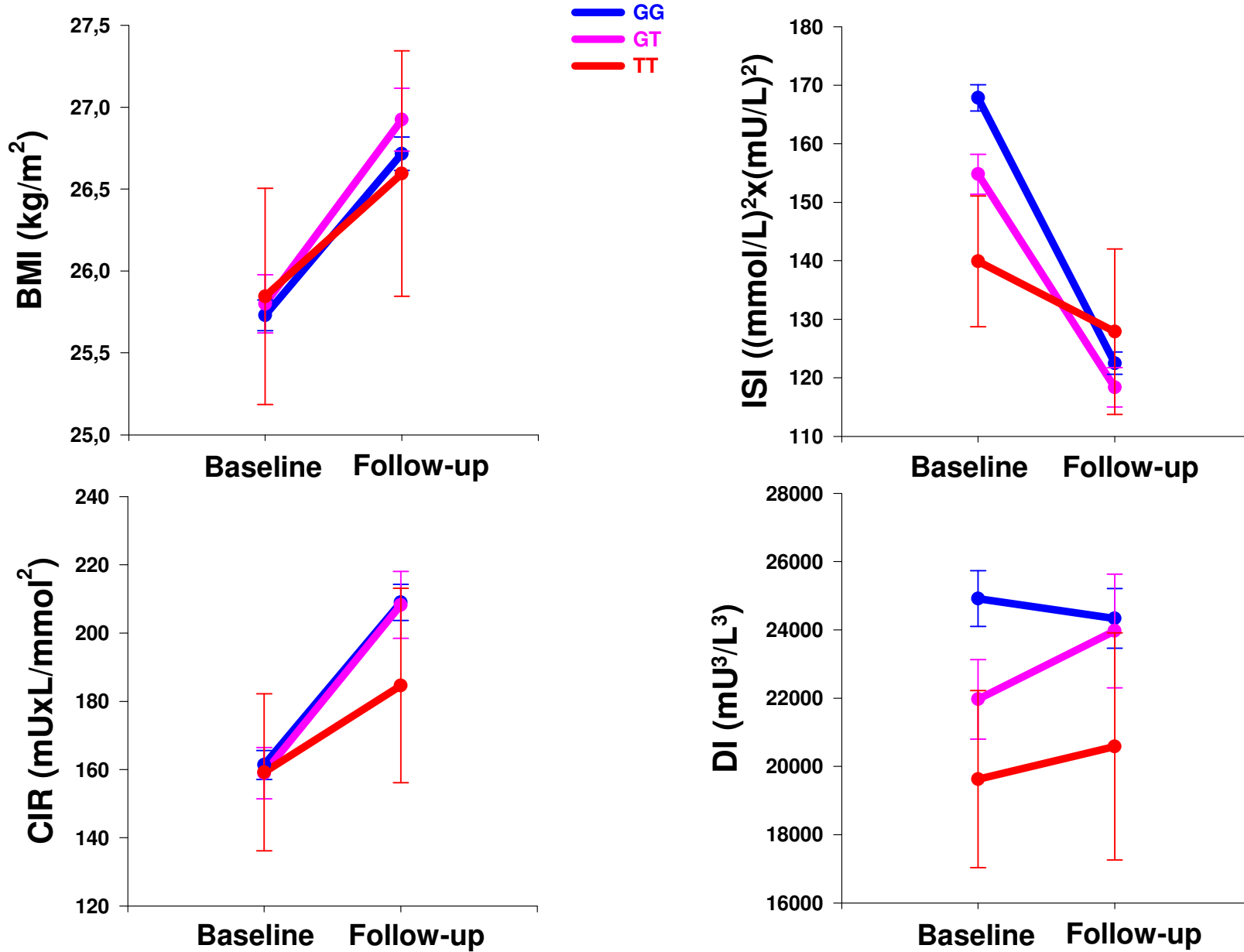
# Supplementary Figure 3

## D *KCNJ11* rs5219



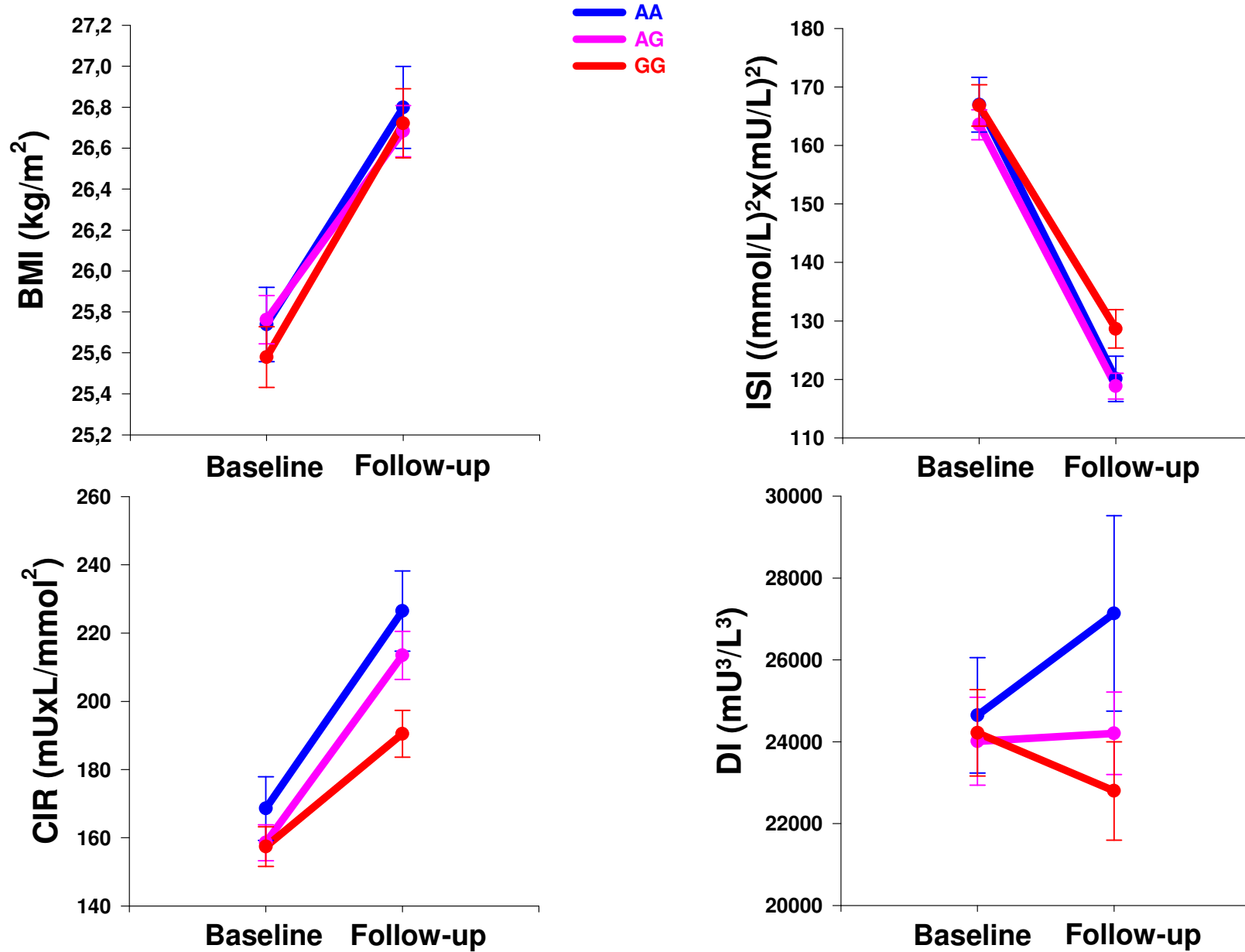
Supplementary Figure 3

**E** *NOTCH2* rs10923931



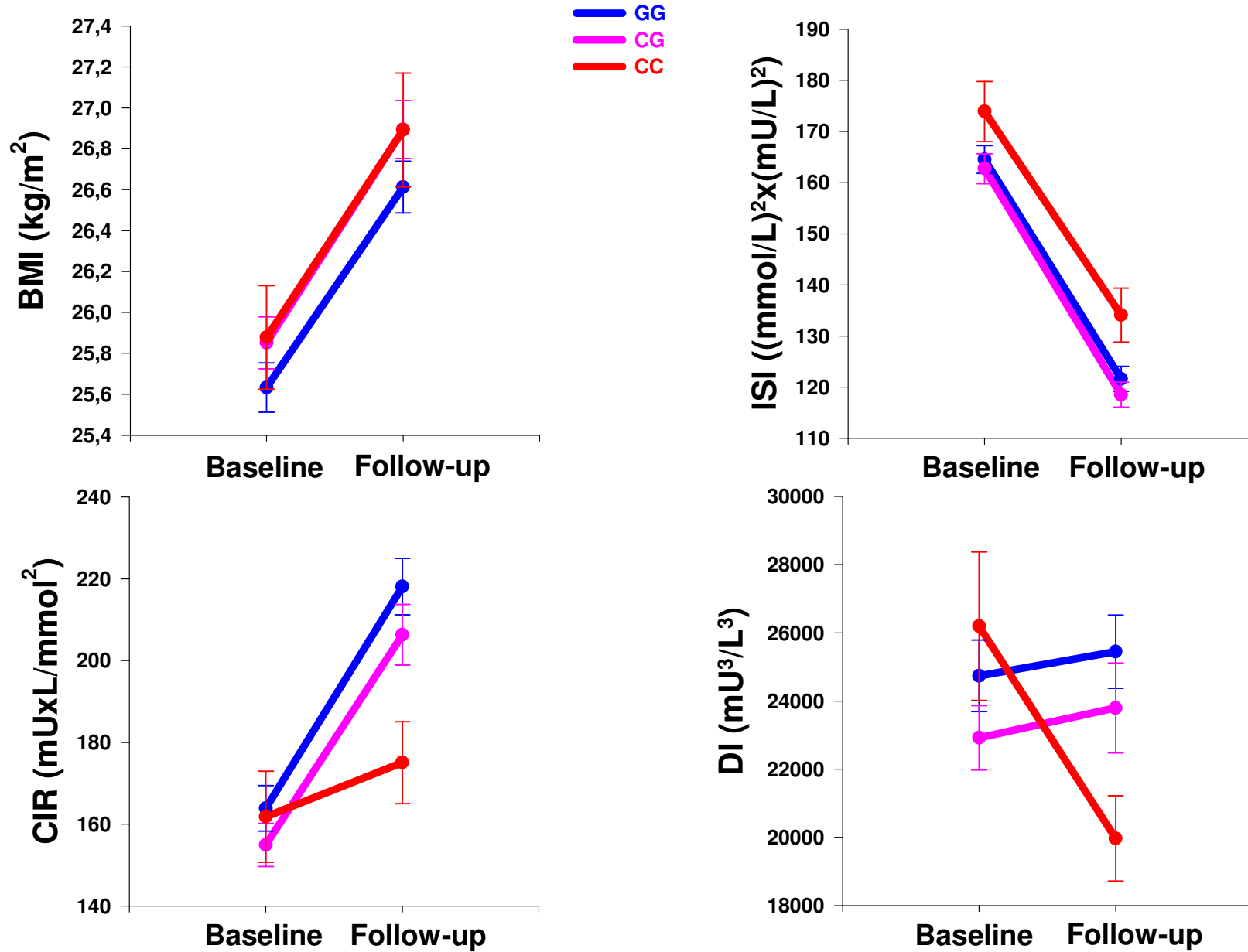
# Supplementary Figure 3

## F *WFS1* rs10010131



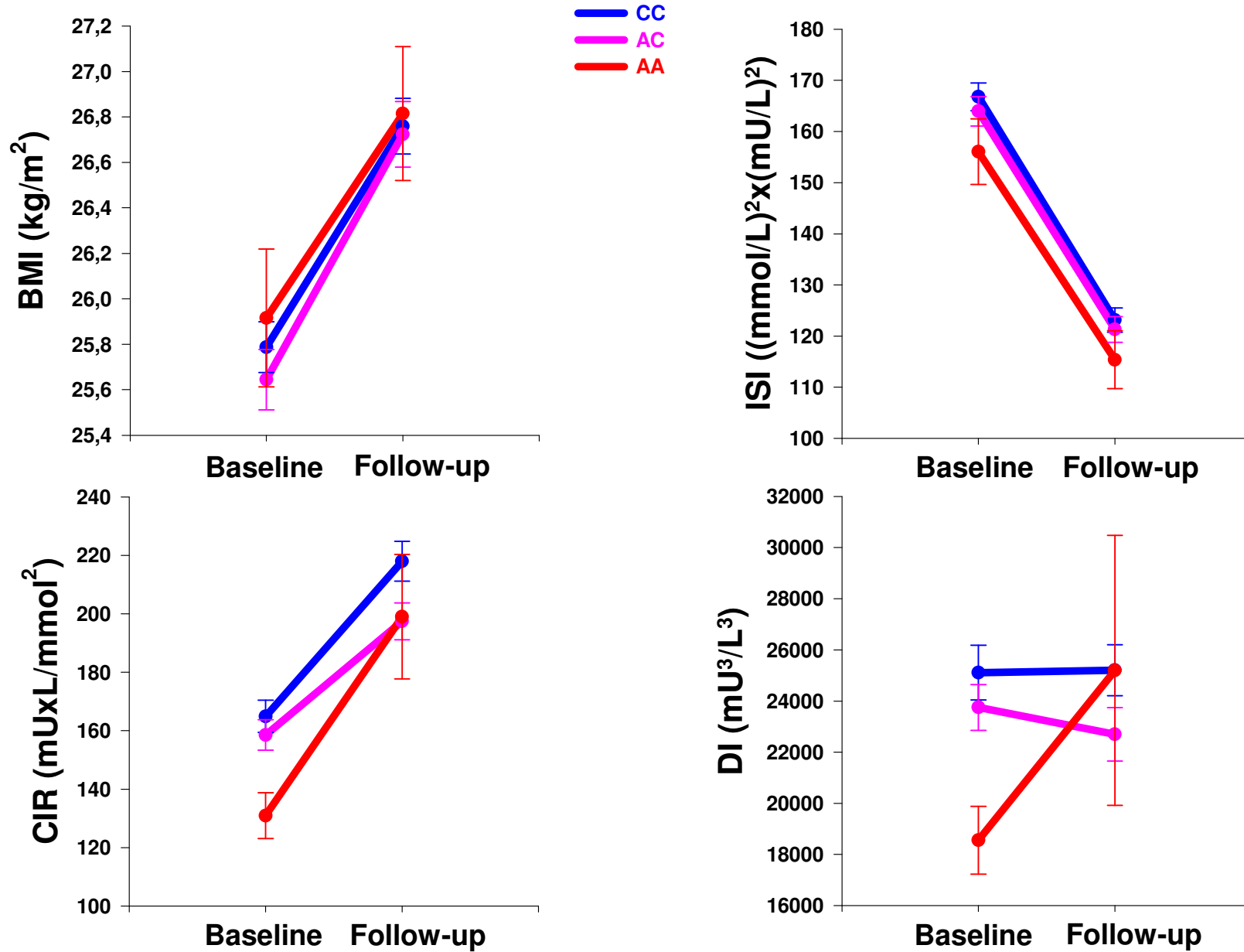
Supplementary Figure 3

**G** *CDKAL1* rs7754840



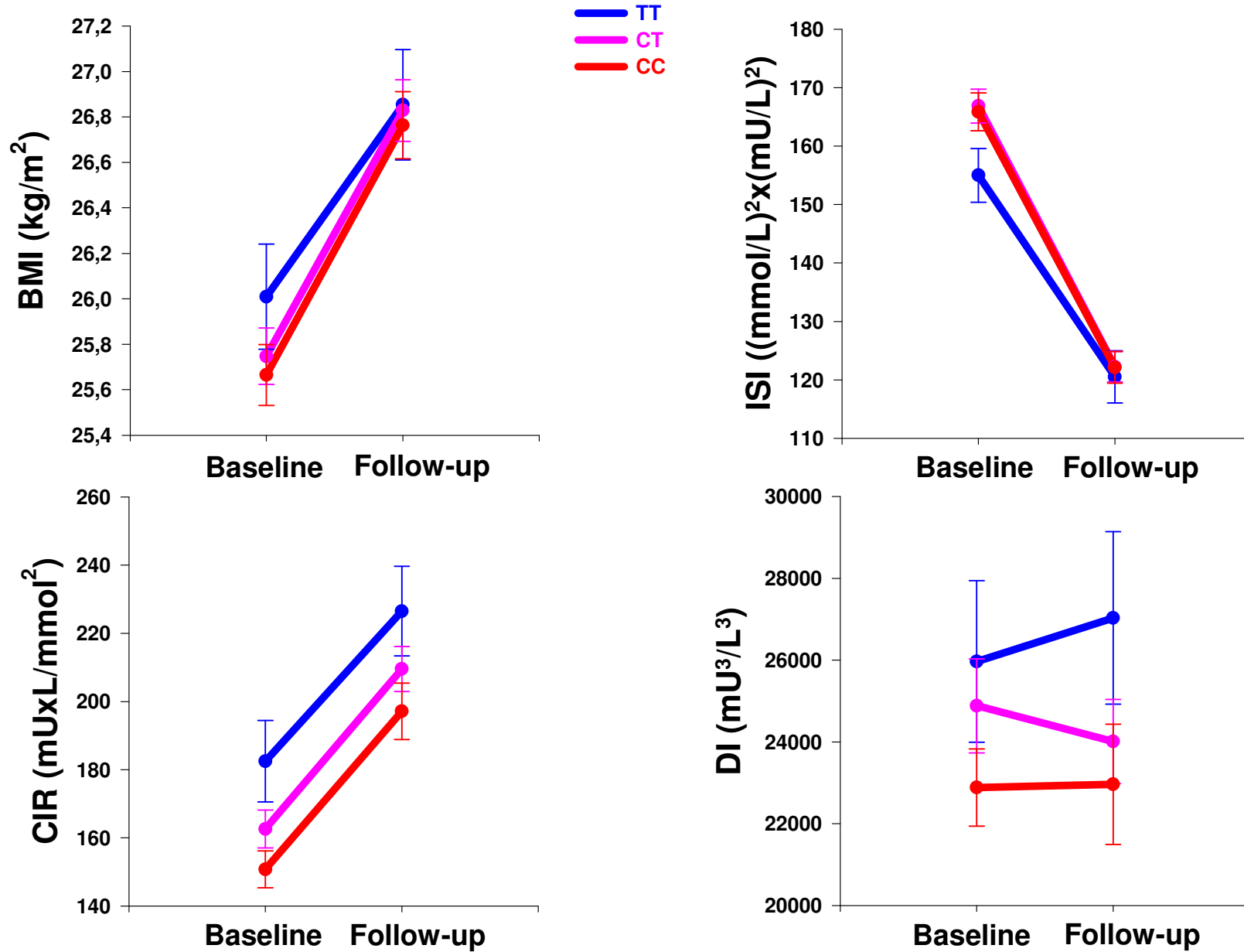
# Supplementary Figure 3

## H *IGF2BP2* rs4402960



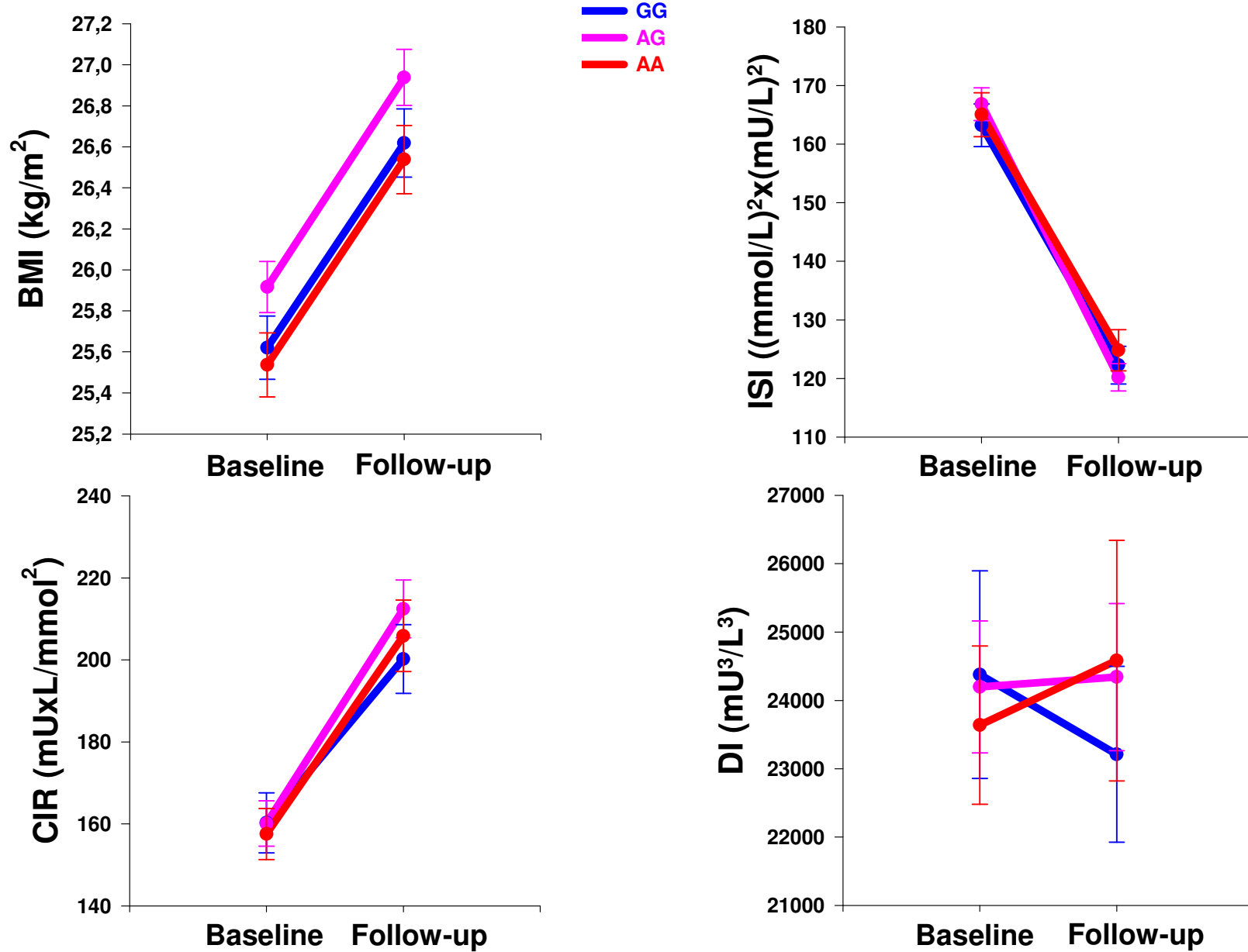
# Supplementary Figure 3

## I *SLC30A8* rs13266634



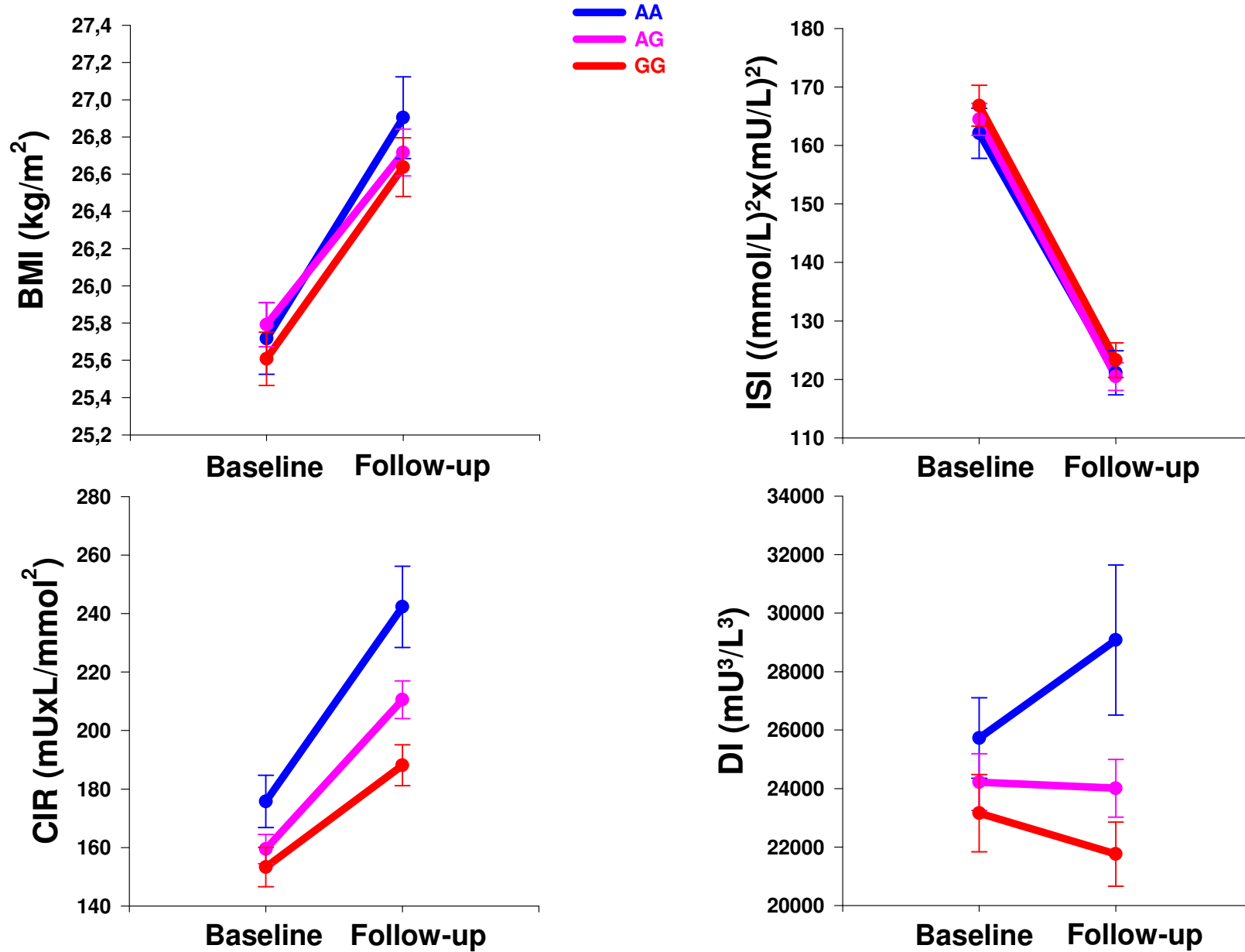
# Supplementary Figure 3

## J *JAZF1* rs864745



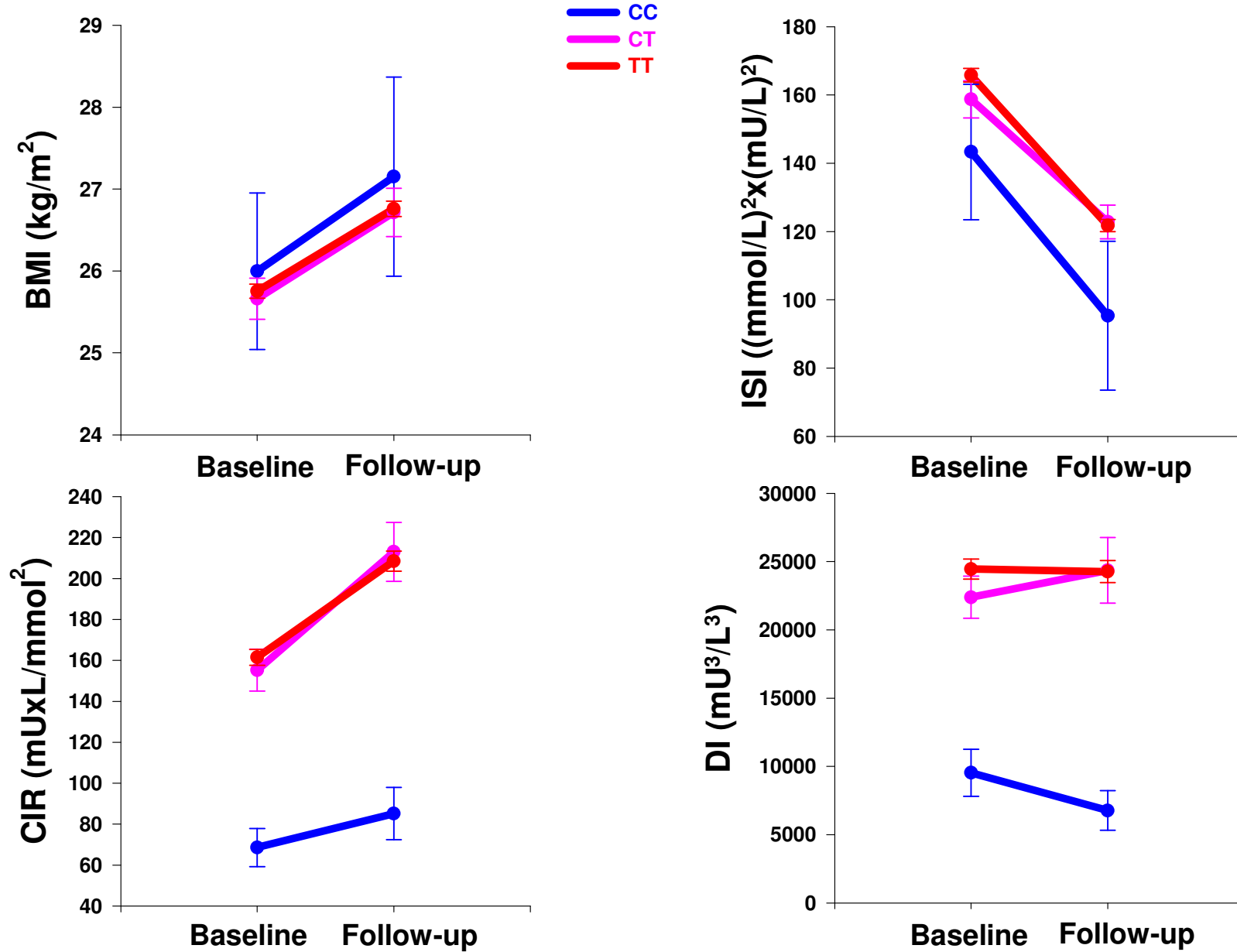
# Supplementary Figure 3

## K *HHEX* rs1111875



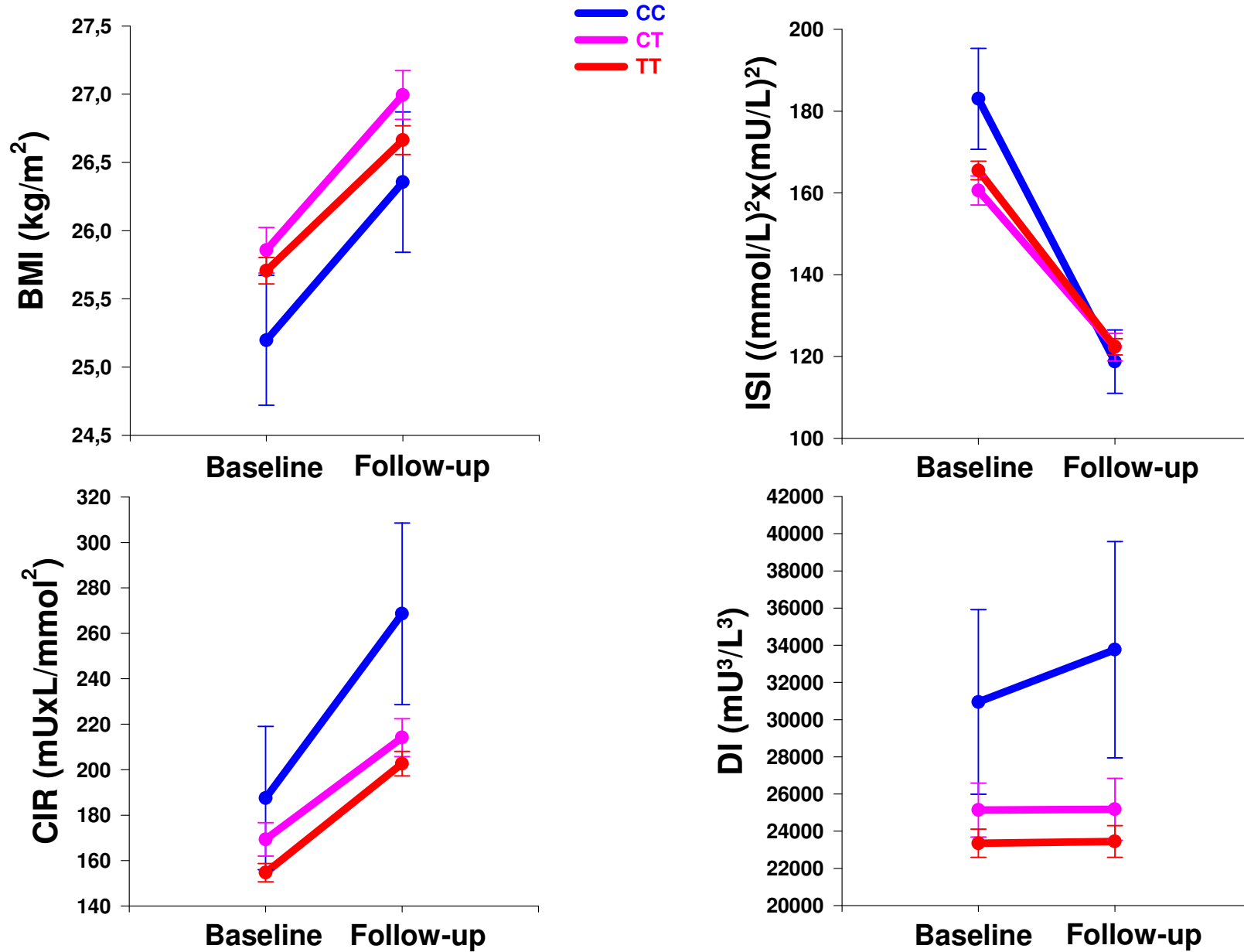
# Supplementary Figure 3

## L *THADA* rs7578597



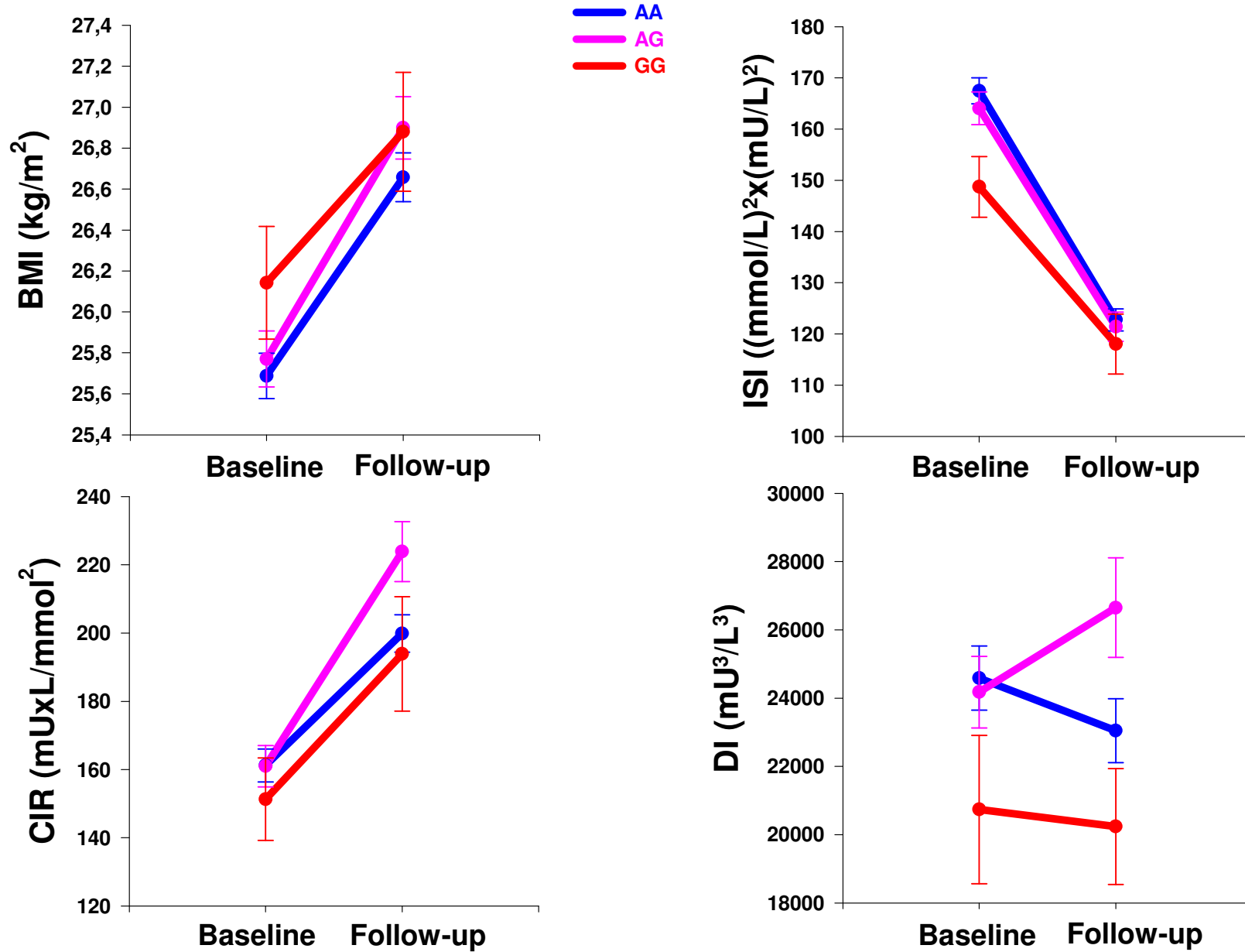
# Supplementary Figure 3

## M *CDKN2A/2B* rs10811661



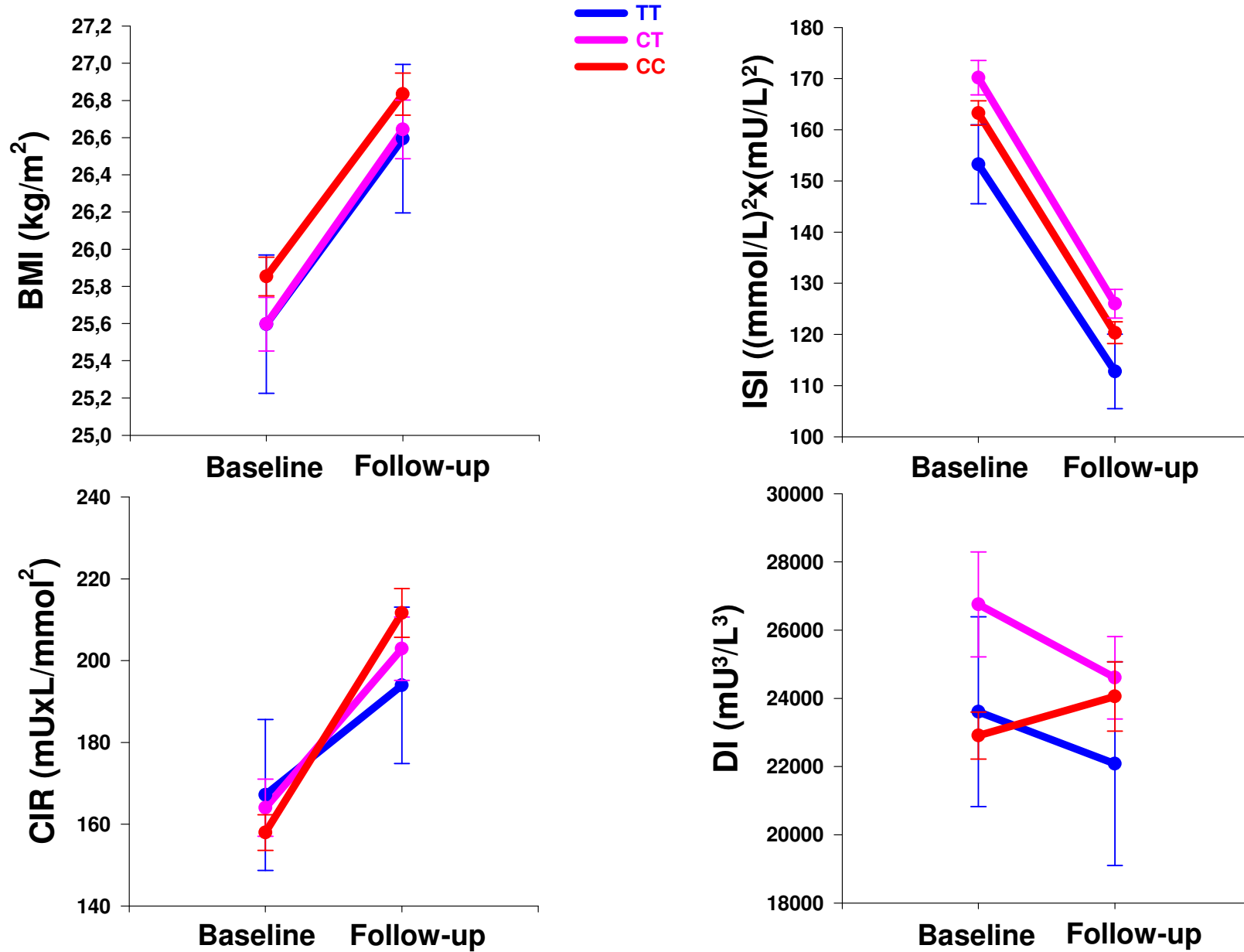
# Supplementary Figure 3

**N** *TSPAN8/LGR5* rs7961581



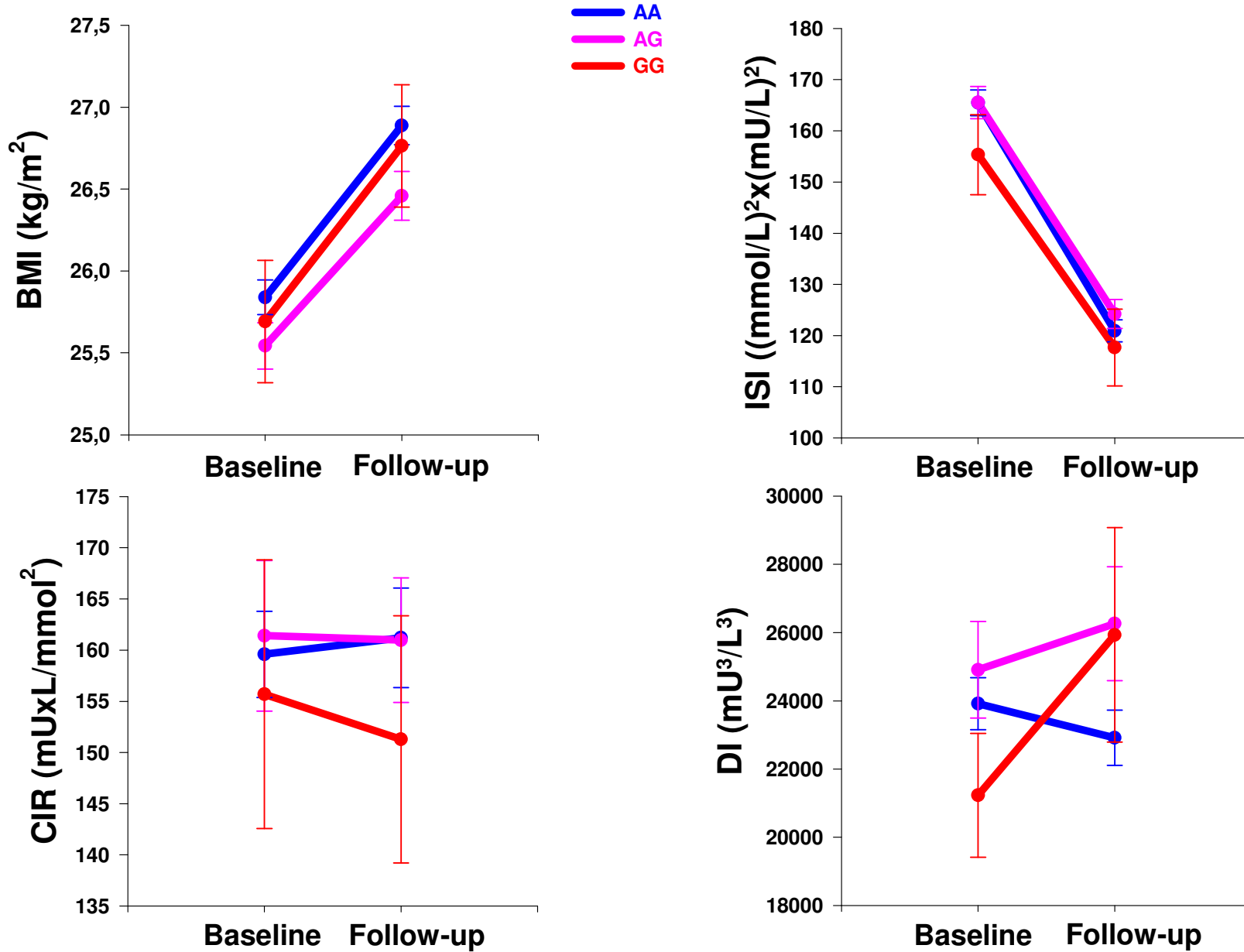
# Supplementary Figure 3

## O *ADAMTS9* rs4607103



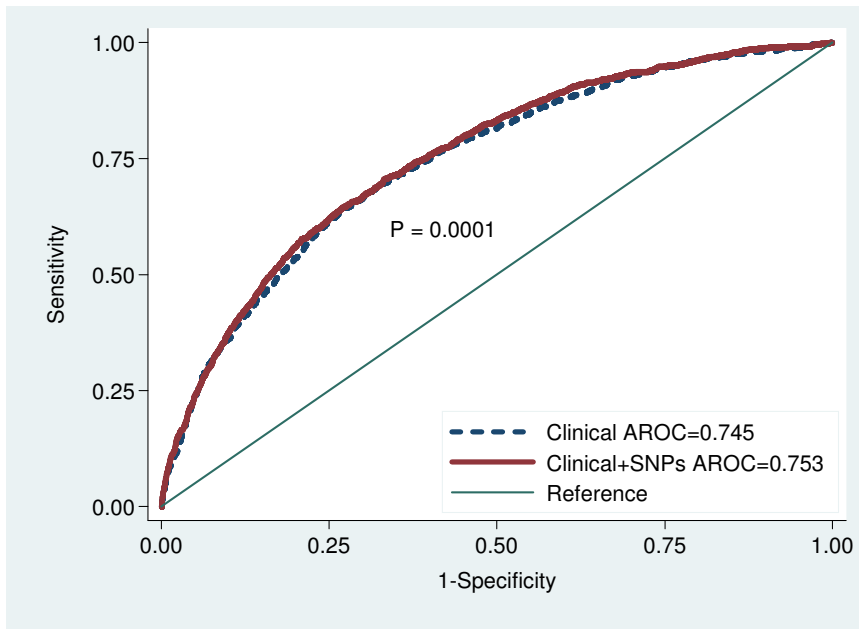
# Supplementary Figure 3

## P *CDC123/CAMK1D* rs12779790

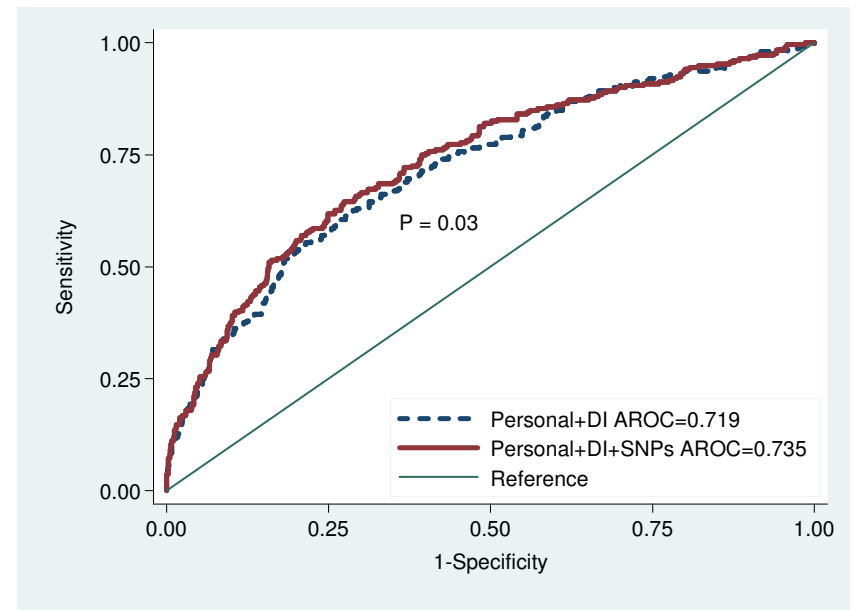


## Supplementary Figure 4

**A**

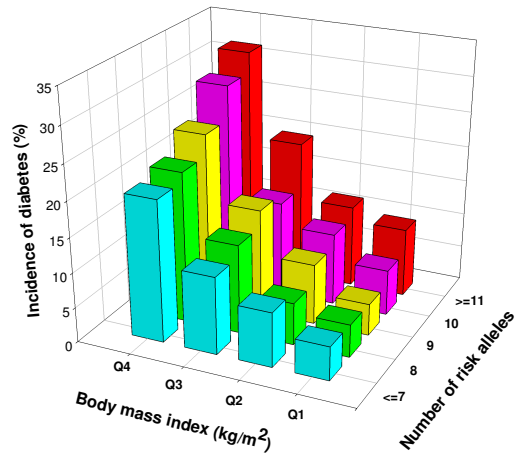


**B**

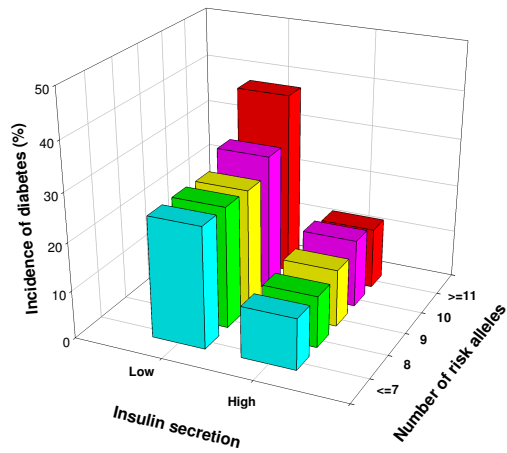


# Supplementary Figure 5

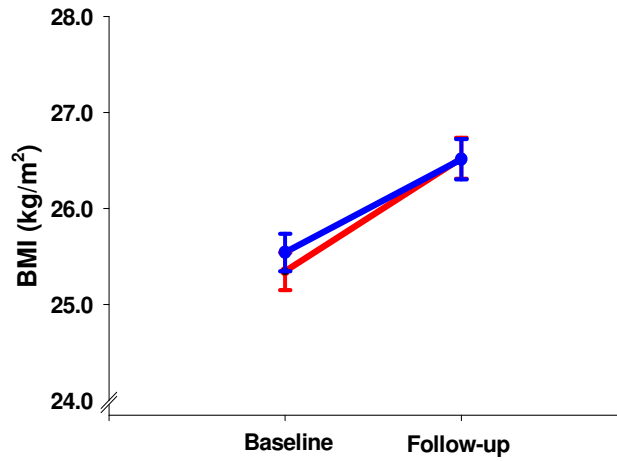
**A**



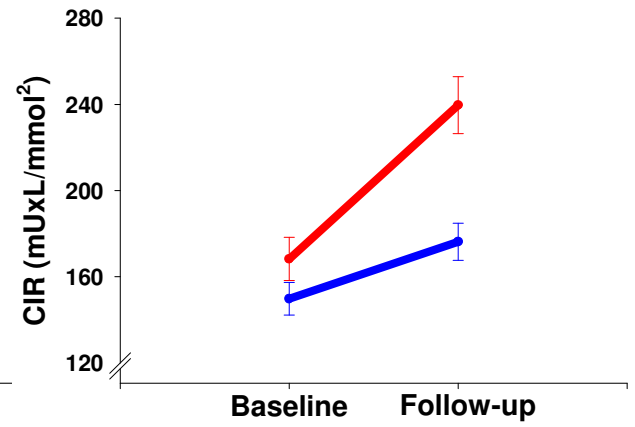
**B**



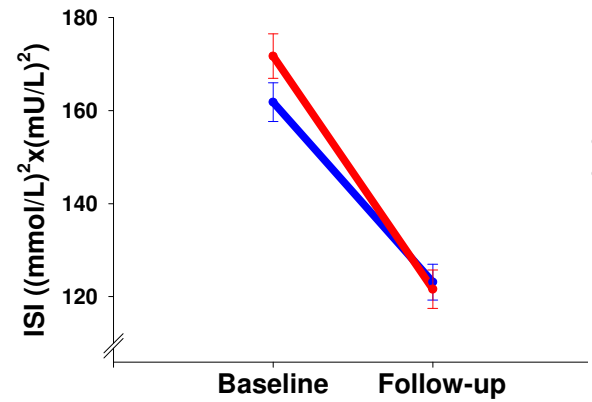
**C**



**E**



**D**



**F**

