Supplementary Information

The distribution of BMI is presented in Figure S3 and shows the nonlinear relationship between BMI and progression to insulin requirement. Compared with those with a BMI of 21-23 kg/m$^2$ (the lowest risk group), participants with BMI<18.5 kg/m$^2$ had a hazard ratio (HR) of 1.4 (1.1-1.9), and those with a 31≤BMI<33 kg/m$^2$ had a HR of 1.3 (1.1-1.7). Then we further divided BMI into four groups based on the World Health Organization definition for obesity in Asians: underweight (BMI<18.5 kg/m$^2$), normal (18.5≤BMI<23.0 kg/m$^2$), overweight (23.0≤BMI<25.0 kg/m$^2$), and obese (25.0+ kg/m$^2$) (1). Since the proportional hazard assumption for baseline HbA1c was not met, we stratified participants into three groups ($HbA_{1c}$<7%, ≥7-9% and ≥9%) to allow for a different hazard function in each group. Therefore, both BMI and baseline $HbA_{1c}$ categories were included as strata variables in Cox regression models, whereas the other covariates were considered to have the same effect across strata.

With regards to the effects of BMI, lower and higher BMI were both associated with increased risk of diabetes progression. With regards to the interaction effects of BMI on rLTL and diabetes progression, rLTL was significantly shorter in progressors from the normal/overweight/obese group, compared with non-progressors. However, the association between rLTL and diabetes progression in the normal BMI group and the obese group was attenuated after adjusting for confounders, while the significance in the overweight group remained unchanged after full adjustment. The significant association between rLTL and diabetes progression was only observed in the overweight group. (HR (95% CI): 1.157 (1.042-1.286), P=0.006). (Table S2)

The whole cohort was divided into three groups based on baseline $HbA_{1c}$ ($HbA_{1c}$<7%, ≥7-9% and ≥9%), and there was a significant difference in mean rLTL between each group (4.67±1.18 vs. 4.51±1.20 vs. 4.38±1.18; P<0.001). The significant difference of rLTL between the three groups did not change after adjusting for age, sex, known diabetes duration and smoking status (P<0.001). Patients who progressed to insulin requirement had significantly shorter rLTL than those who did not in each group, after adjusting for age, sex, diabetes duration and smoking status (4.52±1.18 vs. 4.73±1.18; 4.44±1.15 vs. 4.61±1.26; 4.30±1.16 vs. 4.62±1.21; all P<0.05). We grouped subjects according to baseline $HbA_{1c}$ and further examined the relationship between rLTL and glycaemic progression in three groups separately, we only observe significant associations between rLTL and glycaemic progression in patients with $HbA_{1c}$ ≥ 9% (HR (95% CI): 1.122 (1.037-1.214), P=0.004), which was attenuated once risk factors considered. (Table S2).

The Kaplan-Meier analysis also shows that those from the tertile with the longest rLTL (≥5.092) had a decreased risk of progression to the requirement of insulin treatment (Figure 1). Compared with those with the longest tertile of rLTL, participants from the tertile with the shortest rLTL had a 1.269-fold higher risk of progression to insulin requirement.

Since HDL-Cholesterol was identified as an independent predictor for glycaemic deterioration in European patients, we included HDL-Cholesterol as a predictor with exclusion of TG and LDL-Cholesterol in multivariate Cox analysis. Shorter telomere length was still associated with a higher risk for requirement of insulin (HR (95% CI): 1.052 (1.008-1.098), P=0.021) in the fully adjusted model.

Besides, we compared the results of rLTL calculated based on NTC or QC reference sample. Like the results of rLTL based on NTC, subjects who progressed to requirement of insulin had significantly lower rLTL-QC (-0.21±1.02 vs. -0.03±1.02; P<0.001), compared with those remained on oral antidiabetic drugs during the follow-up period. Each unit decrease of rLTL based on QC materials was associated with a 1.113-times (95%CI: 1.065-1.164) higher risk of progression to insulin requirement. After adjusting for traditional risk factors, the association remained significant (HR (95% CI): 1.083 (1.031-1.139), P=0.002) (Table S7).

Table S1. Competing Risk Regression analysis showing subdistribution HRs of rLTL for glycaemic progression defined as need for insulin treatment.

| Models | Unadjusted model | | Fully adjusted model | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| rLTL in original model | 1.098 (1.056-1.142) | **<0.001** | 1.052 (1.007-1.100) | **0.023** |
| rLTL considering death before DM progression | 1.079 (1.037-1.072) | **<0.001** | 1.053 (1.005-0.736) | **0.029** |

sHR, subdistribution hazards ratio; rLTL, relative leukocyte telomere length calculated by water. Fully adjusted models included age at diagnosis, duration of diabetes, smoking, log(TG), LDL-C, log(ACR), eGFR, sensory neuropathy, retinopathy, use of lipid-lowering drugs, use of RAS inhibitors and use of oral glucose lowering drugs.

Table S2. Multivariate Cox proportional hazards models for the association between baseline telomere length (calculated using NTC) and incident diabetes progression defined as need for insulin use.

| Diabetes progression | Events/Total (%) | Unadjusted model | | Fully adjusted model | |
|---|---|---|---|---|---|
| | | Hazard Ratio (95% CI) | P value | Hazard Ratio (95% CI) | P value |
| Overall | 1803/3937 | 1.098 (1.056-1.142) | **<0.001** | 1.052 (1.007-1.100) | **0.023** |
| Women | 964/2166 | 1.149 (1.089-1.212) | **<0.001** | 1.119 (1.054-1.187) | **<0.001** |
| Men | 839/1771 | 1.040 (0.982-1.102) | 0.179 | 0.975 (0.912-1.042) | 0.457 |
| Young age at diagnosis | | | | | |
| < 40 years | 443/748 | 1.088 (1.041-1.138) | **<0.001** | 1.037 (0.987-1.090) | 0.146 |
| 40+ years | 1360/3188 | 1.156 (1.063-1.258) | **0.001** | 1.146 (1.038-1.267) | **0.007** |
| BMI kg/m$^2$ | | | | | |
| <18.5 | 46/95 | 1.212 (0.925-1.588) | 0.164 | 1.130 (0.814-1.567) | 0.466 |
| 18.5-23 | 478/1064 | 1.070 (0.992-1.153) | 0.079 | 0.992 (0.912-1.078) | 0.842 |
| 23-25 | 383/841 | 1.180 (1.088-1.281) | **<0.001** | 1.157 (1.042-1.286) | **0.006** |
| ≥25 | 892/1917 | 1.071 (1.011-1.134) | **0.020** | 1.042 (0.979-1.108) | 0.195 |
| $HbA_{1C}$ | | | | | |
| < 7% | 555/1904 | 1.062 (0.987-1.142) | 0.107 | 1.020 (0.941-1.106) | 0.624 |
| ≥7-9% | 784/1412 | 1.038 (0.978-1.101) | 0.219 | 1.052 (0.986-1.122) | 0.127 |
| ≥9% | 464/621 | 1.122 (1.037-1.214) | **0.004** | 1.075 (0.982-1.178) | 0.118 |

BMI and baseline HbA1c categories were included as strata variables. BMI was categorised as four groups (<18.5, 18.5-23, 23-25 and ≥25 kg/m$^2$) and baseline HbA1c was categorized as three groups (<7%, ≥ 7-9% and ≥ 9%). Fully adjusted models included age at diagnosis, duration of diabetes, smoking, log(TG), LDL-C, log(ACR), eGFR, sensory neuropathy, retinopathy, use of lipid-lowering drugs, use of RAS inhibitors and use of oral glucose-lowering drugs.

Table S3. Cox regression analysis for the association between baseline relative telomere length and glycaemic progression defined as actual use of insulin

| Variables | Unadjusted model | | Fully adjusted model | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| rLTL | 1.121 (1.075-1.170) | <0.001 | 1.065 (1.016-1.117) | **0.009** |
| Age at diagnosis (per 1 year) | | | 0.967 (0.961-0.973) | **<0.001** |
| Duration of diabetes (per 1 year) | | | 1.023 (1.013-1.032) | **<0.001** |
| Smoking | | | | |
| Ex-smoker | | | 1.213 (1.045-1.408) | **0.011** |
| Current smoker | | | 1.097 (0.935-1.288) | 0.256 |
| log (triglyceride) | | | 1.105 (0.853-1.431) | 0.452 |
| LDL-C | | | 0.897 (0.845-0.952) | **<0.001** |
| log urinary ACR | | | 1.480 (1.351-1.622) | **<0.001** |
| eGFR | | | 0.988 (0.984-0.991) | **<0.001** |
| Sensory neuropathy | | | 1.245 (1.089-1.425) | **0.001** |
| Retinopathy | | | 1.257 (1.100-1.437) | **0.001** |
| Use of oral glucose-lowering drugs | | | 1.191 (1.050-1.352) | **0.007** |
| Use of lipid-lowering drugs | | | 1.001 (0.844-1.188) | 0.991 |
| Use of RAS inhibitors | | | 1.128 (0.969-1.313) | 0.120 |

BMI and baseline HbA1c categories were included as strata variables. BMI was categorised as four groups (<18.5, 18.5-23, 23-25 and ≥25 kg/m$^2$) and baseline HbA1c was categorized as three groups (<7%, ≥ 7-9% and ≥ 9%).

Abbreviations: rLTL, relative leukocyte telomere length calculated by water; LDL-C, low-density lipoprotein cholesterol; ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

Table S4. The relationship between baseline relative telomere length and glycaemic exposure during follow-up.

| Variables | Unadjusted model | | Fully adjusted model | |
|---|---|---|---|---|
| | Beta (95% CI) | P value | Beta (95% CI) | P value |
| (Intercept) | 1.116 (1.054-1.179) | <0.001 | 0.185 (0.365-0.004) | **0.045** |
| rLTL | -0.048 (-0.061- -0.035) | <0.001 | -0.018 (-0.007--0.029) | **0.001** |
| Age at diagnosis (per 1 year) | | | 0.000 (0.001--0.001) | 0.861 |
| BMI ($kg/m^2$) | | | 0.004 (0.007-0.001) | **0.017** |
| HbA1c (%) | | | 0.017 (0.025-0.009) | **<0.001** |
| Duration of diabetes (per 1 year) | | | -0.001 (0.002--0.003) | 0.676 |
| Smoking | | | | |
| Ex-smoker | | | 0.018 (0.052--0.015) | 0.289 |
| Current smoker | | | 0.070 (0.106-0.033) | **<0.001** |
| log (triglyceride) | | | -0.045 (0.012--0.102) | 0.126 |
| LDL-C | | | -0.003 (0.010--0.017) | 0.615 |
| log urinary ACR | | | 0.006 (0.029--0.017) | 0.614 |
| eGFR | | | 0.001 (0.002-0.001) | **<0.001** |
| Sensory neuropathy | | | -0.033 (0.001--0.067) | 0.057 |
| Retinopathy | | | -0.025 (0.006--0.057) | 0.117 |
| Use of oral glucose lowering drugs | | | -0.039 (-0.010--0.067) | **0.008** |
| Use of lipid-lowering drugs | | | -0.069 (-0.037--0.100) | **<0.001** |
| Use of RAS inhibitors | | | -0.016 (0.016--0.048) | 0.327 |
| Follow-up time (per 1 year) | | | 0.053 (0.056-0.050) | **<0.001** |

Abbreviations: rLTL, relative leukocyte telomere length calculated by water; LDL-C, low-density lipoprotein cholesterol; ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

Table S5. Cox regression analysis for association between baseline absolute telomere length and glycaemic progression defined as need for insulin treatment.

| Variables | Unadjusted model | | Fully adjusted model | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Absolute LTL (per kb) | 1.688 (1.353-2.105) | <0.001 | 1.332 (1.040-1.705) | **0.023** |
| Age at diagnosis (per 1 year) | | | 0.971 (0.966-0.976) | **<0.001** |
| Duration of diabetes (per 1 year) | | | 1.020 (1.011-1.029) | **<0.001** |
| Smoking | | | | |
| Ex-smoker | | | 1.248 (1.088-1.430) | **0.002** |
| Current smoker | | | 1.158 (1.003-1.338) | **0.045** |
| log (triglyceride) | | | 1.323 (1.044-1.675) | **0.020** |
| LDL-C | | | 0.936 (0.886-0.987) | **0.015** |
| log urinary ACR | | | 1.373 (1.262-1.495) | **<0.001** |
| eGFR | | | 0.991 (0.988-0.994) | **<0.001** |
| Sensory neuropathy | | | 1.268 (1.120-1.435) | **<0.001** |
| Retinopathy | | | 1.235 (1.092-1.396) | **0.001** |
| Use of oral glucose lowering drugs | | | 1.284 (1.143-1.443) | **<0.001** |
| Use of lipid-lowering drugs | | | 1.049 (0.901-1.221) | 0.542 |
| Use of RAS inhibitors | | | 1.147 (0.999-1.318) | 0.052 |

BMI and baseline HbA1c categories were included as strata variables. BMI was categorised as four groups (<18.5, 18.5-23, 23-25 and ≥25 kg/m$^2$) and baseline HbA1c was categorized as three groups (<7%, ≥ 7-9% and ≥ 9%).

Abbreviations: absolute LTL, absolute leukocyte telomere length estimated using telseq; LDL-C, low-density lipoprotein cholesterol; ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

Table S6 The sensitivity analysis of association between shorter rLTL at baseline and diabetes progression, stratified by DM duration <5, 5-10, >10 years.

| DM duration at baseline | Events/Total (%) | Unadjusted Model | | Fully adjusted Model | |
|---|---|---|---|---|---|
| | | HR (95% CI) | P value | HR (95% CI) | P value |
| ≤5 years | 919/2326 | 1.065 (1.006-1.127) | **0.031** | 1.048 (0.985-1.115) | **0.140** |
| 5-10 years | 448/870 | 1.040 (0.962-1.123) | 0.319 | 1.055 (0.966-1.152) | 0.231 |
| >10 years | 436/740 | 1.116 (1.030-1.208) | **0.007** | 1.024 (0.930-1.126) | 0.633 |

HR, hazards ratio for each unit deceased in rLTL; rLTL, relative leukocyte telomere length calculated by water. Fully adjusted models included age at diagnosis, duration of diabetes, smoking, BMI, log(TG), LDL-C, log(ACR), eGFR, HbA1c, sensory neuropathy, retinopathy, use of lipid-lowering drugs, use of RAS inhibitors and use of oral glucose lowering drugs.

Table S7 Cox regression analysis for association between baseline relative telomere length and glycaemic progression defined as need for insulin treatment among 3868 subjects (after exclusion of subjects with GAD+)

| Variables | Unadjusted model | | Fully adjusted model | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| rLTL | 1.099 (1.057-1.144) | **<0.001** | 1.052 (1.006-1.100) | **0.026** |
| Age at diagnosis (per 1 year) | | | 0.971 (0.966-0.976) | **<0.001** |
| Duration of diabetes (per 1 year) | | | 1.021 (1.012-1.030) | **<0.001** |
| Smoking | | | | |
| Ex-smoker | | | 1.244 (1.084-1.427) | **0.002** |
| Current smoker | | | 1.150 (0.994-1.329) | 0.060 |
| log (triglyceride) | | | 1.383 (1.088-1.756) | **0.008** |
| LDL-C | | | 0.932 (0.883-0.985) | **0.012** |
| log urinary ACR | | | 1.381 (1.268-1.504) | **<0.001** |
| eGFR | | | 0.991 (0.988-0.994) | **<0.001** |
| Sensory neuropathy | | | 1.275 (1.126-1.444) | **<0.001** |
| Retinopathy | | | 1.240 (1.096-1.404) | **<0.001** |
| Use of oral glucose lowering drugs | | | 1.268 (1.127-1.426) | **<0.001** |
| Use of lipid-lowering drugs | | | 1.057 (0.906-1.232) | 0.482 |
| Use of RAS inhibitors | | | 1.155 (1.005-1.329) | **0.043** |

BMI and baseline HbA1c categories were included as strata variables. BMI was categorised as four groups (<18.5, 18.5-23, 23-25 and ≥25 kg/m$^2$) and baseline HbA1c was categorized as three groups (<7%, ≥ 7-9% and ≥ 9%).

Abbreviations: rLTL, relative leukocyte telomere length calculated by water; LDL-C, low-density lipoprotein cholesterol; ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

Table S8. The genetic variants for Mendelian Randomization analysis of telomere length (exposure) and glyacemic progression (outcome)

| SNP | Gene | Chr | Position | Effect Allele | Ref allele | Beta* | SE* | P value* | Beta# | SE# | P value# |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs10857352 | NAF1 | 4 | 164101482 | A | G | -0.031 | 0.027 | 2.45E-01 | -0.064 | 0.011 | 4.85E-09 |
| rs12415148 | OBFC1 | 10 | 105680586 | T | C | -0.050 | 0.048 | 2.98E-01 | -0.204 | 0.020 | 2.78E-25 |
| rs227080 | ATM | 11 | 108247888 | G | A | -0.035 | 0.023 | 1.32E-01 | -0.060 | 0.009 | 1.87E-10 |
| rs2293607 | TERC | 3 | 169482335 | C | T | -0.053 | 0.023 | 2.19E-02 | -0.120 | 0.009 | 7.57E-39 |
| rs28365964 | TERF1 | 8 | 73920883 | T | C | -0.239 | 0.109 | 2.85E-02 | -0.270 | 0.035 | 6.96E-15 |
| rs3219104 | PARP1 | 1 | 226562621 | A | C | -0.050 | 0.024 | 3.31E-02 | -0.074 | 0.009 | 2.23E-16 |
| rs41293836 | TINF2 | 14 | 24721327 | C | T | -0.216 | 0.040 | 9.11E-08 | -0.233 | 0.017 | 2.47E-42 |
| rs41309367 | RTEL1 | 20 | 62309554 | T | C | -0.016 | 0.026 | 5.24E-01 | -0.058 | 0.010 | 1.16E-08 |
| rs7705526 | TERT | 5 | 1285974 | C | A | -0.023 | 0.023 | 3.22E-01 | -0.118 | 0.009 | 2.61E-38 |
| rs7776744 | POT1 | 7 | 124599749 | G | A | -0.001 | 0.023 | 9.70E-01 | -0.058 | 0.009 | 2.51E-10 |

SNP, single nucleotide polymorphism; Chr, chromosome; Ref allele, reference allele; EAF, effect allele frequency; Beta, SE, P-value, assocation with telomere length in Singaporean GWAS study. *indicates analysis conducted in Hong Kong Diabetes Registry. #indicates the extracted data from original GWAS study.

Table S9 the relationship between genetically determined telomere length and glycaemic progression defiend as insulin requirement.

| | Outcome | Exposure | Method | No of SNPs | OR (95%CI)* | P value |
|---|---|---|---|---|---|---|
| 1 | Insulin requirement | Telomere length | MR Egger | 10 | 1.541 (0.804-2.954) | 0.229 |
| 2 | Insulin requirement | Telomere length | Maximum likelihood | 10 | 1.382 (1.016-1.878) | **0.039** |
| 3 | Insulin requirement | Telomere length | Weighted median | 10 | 1.351 (0.903-2.021) | 0.144 |
| 4 | Insulin requirement | Telomere length | Weighted mode | 10 | 1.223 (0.721-2.074) | 0.474 |
| 5 | Insulin requirement | Telomere length | Inverse variance weighted (multiplicative random effects) | 10 | 1.384 (1.124-1.704) | **0.002** |
| 6 | Insulin requirement | Telomere length | Inverse variance weighted (fixed effects) | 10 | 1.384 (1.020-1.879) | **0.037** |

* indicates odds for glycaemic progression per 1-unit decreased in genetically determined telomere length. Glycaemic progression was defined as the need for insulin requirement.

Table S10 the relationship between genetically determined telomere length and glycaemic progression defiend as actual insulin use.

| | Outcome | Exposure | Method | No of SNPs | OR (95%CI)* | P value |
|---|---|---|---|---|---|---|
| 1 | Insulin use | Telomere length | MR Egger | 10 | 1.264 (0.651-2.452) | 0.509 |
| 2 | Insulin use | Telomere length | Maximum likelihood | 10 | 1.367 (0.999-1.870) | 0.051 |
| 3 | Insulin use | Telomere length | Weighted median | 10 | 1.393 (0.913-2.127) | 0.124 |
| 4 | Insulin use | Telomere length | Weighted mode | 10 | 1.640 (0.863-3.113) | 0.165 |
| 5 | Insulin use | Telomere length | Inverse variance weighted (multiplicative random effects) | 10 | 1.374 (1.038-1.818) | 0.026 |
| 6 | Insulin use | Telomere length | Inverse variance weighted (fixed effects) | 10 | 1.374 (1.006-1.876) | 0.046 |

* indicates odds for glycaemic progression per 1-unit decreased in genetically determined telomere length. Glycaemic progression was defined as the need for actual insulin use.

Table S11 Cox regression showing the association between rLTL calculated based on QC materials and glycaemic progression.

| Variables | Unadjusted model | | Fully adjusted model | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| rLTL based on QC | 1.113 (1.065-1.164) | **<0.001** | 1.083 (1.031-1.139) | **0.002** |
| Age at diagnosis (per 1 year) | | | 0.970 (0.965-0.976) | **<0.001** |
| Duration of diabetes (per 1 year) | | | 1.020 (1.011-1.029) | **<0.001** |
| Smoking | | | | |
| Ex-smoker | | | 1.247 (1.088-1.430) | **0.002** |
| Current smoker | | | 1.155 (1.000-1.334) | **0.050** |
| log (triglyceride) | | | 1.331 (1.051-1.686) | **0.018** |
| LDL-C | | | 0.933 (0.883-0.984) | **0.011** |
| log urinary ACR | | | 1.370 (1.259-1.492) | **<0.001** |
| eGFR | | | 0.991 (0.988-0.994) | **<0.001** |
| Sensory neuropathy | | | 1.265 (1.118-1.432) | **<0.001** |
| Retinopathy | | | 1.237 (1.094-1.399) | **0.001** |
| Use of oral glucose-lowering drugs | | | 1.289 (1.148-1.448) | **<0.001** |
| Use of lipid-lowering drugs | | | 1.049 (0.901-1.221) | 0.539 |
| Use of RAS inhibitors | | | 1.144 (0.996-1.314) | 0.057 |

BMI and baseline HbA1c categories were included as strata variables. BMI was categorised as four groups (<18.5, 18.5-23, 23-25 and ≥25 kg/m$^2$) and baseline HbA1c was categorized as three groups (<7%, ≥ 7-9% and ≥ 9%).

Abbreviations: rLTL, relative leukocyte telomere length calculated by QC materials; LDL-C, low-density lipoprotein cholesterol; ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

Table S12. Hazard ratio (95% CI) for glycaemic progression according to tertiles of rLTL.

| Variables | Unadjusted model | | Fully adjusted model | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Tertile 1 | 1.269 (1.131-1.424) | **<0.001** | 1.091 (0.963-1.236) | 0.170 |
| Tertile 2 | 1.155 (1.027-1.298) | **0.016** | 1.071 (0.946-1.212) | 0.277 |
| Tertile 3 | Reference | | | |
| Age at diagnosis (per 1 year) | | | 0.971 (0.966-0.976) | **<0.001** |
| Duration of diabetes (per 1 year) | | | 1.021 (1.012-1.030) | **<0.001** |
| Smoking | | | | |
| Ex-smoker | | | 1.249 (1.089-1.431) | **0.001** |
| Current smoker | | | 1.161 (1.006-1.340) | **0.042** |
| log (triglyceride) | | | 1.318 (1.041-1.670) | **0.022** |
| LDL-C | | | 0.936 (0.887-0.988) | **0.017** |
| log urinary ACR | | | 1.379 (1.267-1.502) | **<0.001** |
| eGFR | | | 0.991 (0.988-0.994) | **<0.001** |
| Sensory neuropathy | | | 1.267 (1.119-1.434) | **<0.001** |
| Retinopathy | | | 1.235 (1.092-1.396) | **0.001** |
| Use of oral glucose-lowering drugs | | | 1.282 (1.141-1.440) | **<0.001** |
| Use of lipid-lowering drugs | | | 1.041 (0.894-1.212) | 0.605 |
| Use of RAS inhibitors | | | 1.148 (0.999-1.318) | 0.051 |

BMI and baseline HbA1c categories were included as strata variables. BMI was categorised as four groups (<18.5, 18.5-23, 23-25 and ≥25 kg/m$^2$) and baseline HbA1c was categorized as three groups (<7%, ≥ 7-9% and ≥ 9%).

Abbreviations: rLTL, relative leukocyte telomere length calculated by water; LDL-C, low-density lipoprotein cholesterol; ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

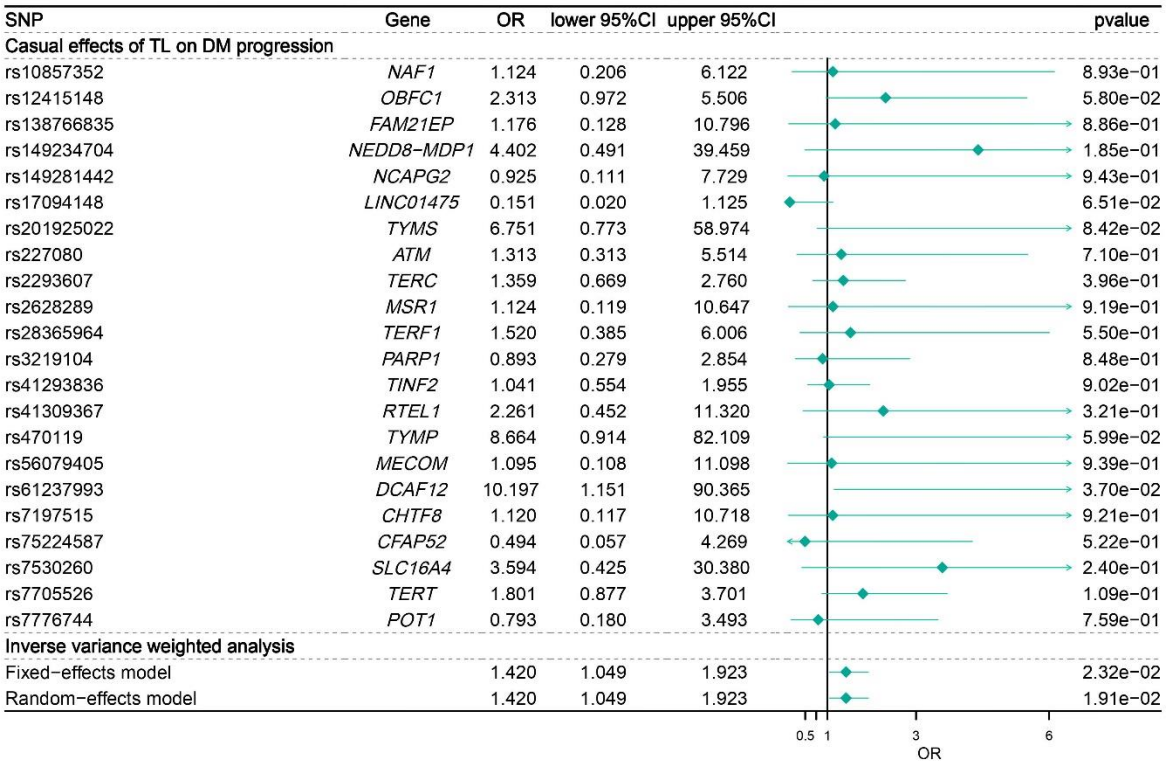


Figure S1. Odds ratio for glycaemic progression per 1-unit decreased in genetically determined relative leukocyte telomere length using 22 SNPs at significance $<1*10^{-5}$.

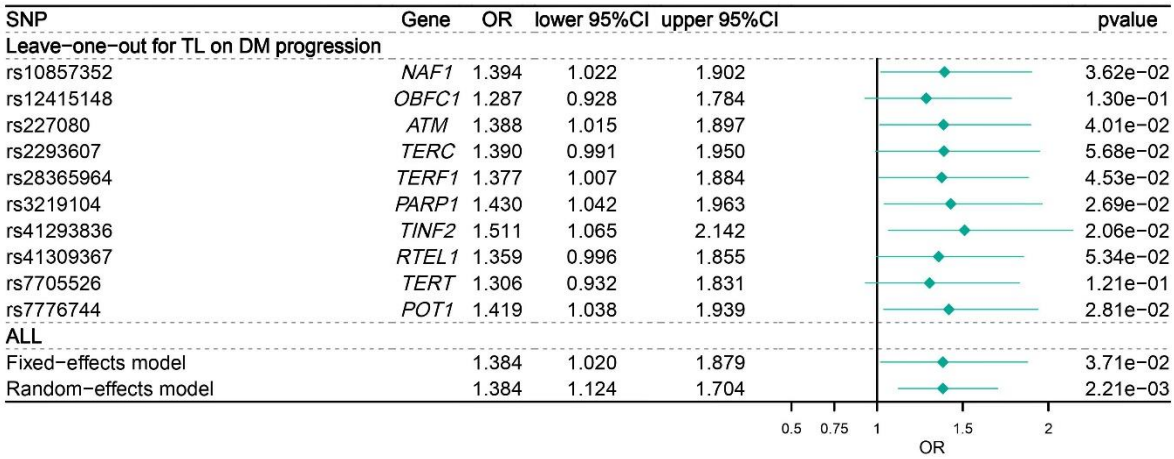


Figure S2. Leave-one-out sensitivity analysis for the final instrument variable set. The solid lines represent 95% confidence intervals. Glycaemic progression was defined as need for insulin treatment.

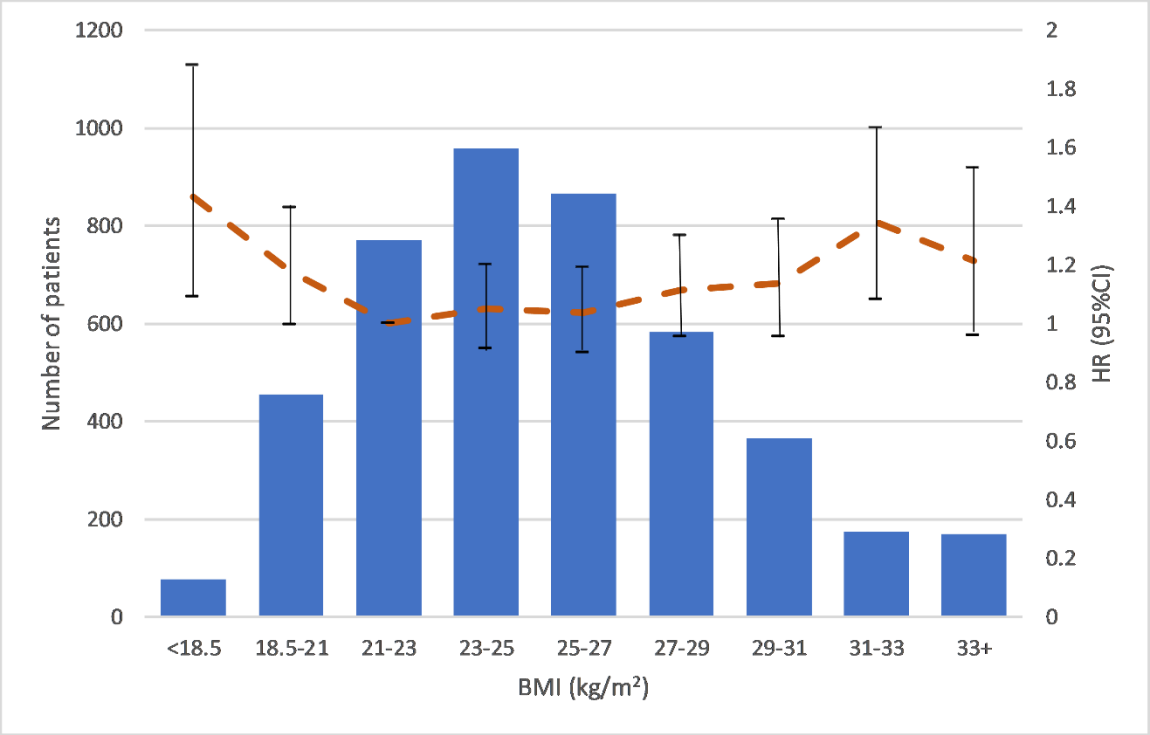


Figure S3 Association between BMI at baseline and progression to requirement of insulin treatment. Distribution of BMI and hazard ratios with BMI 21-23 kg/m$^2$ as the reference group.

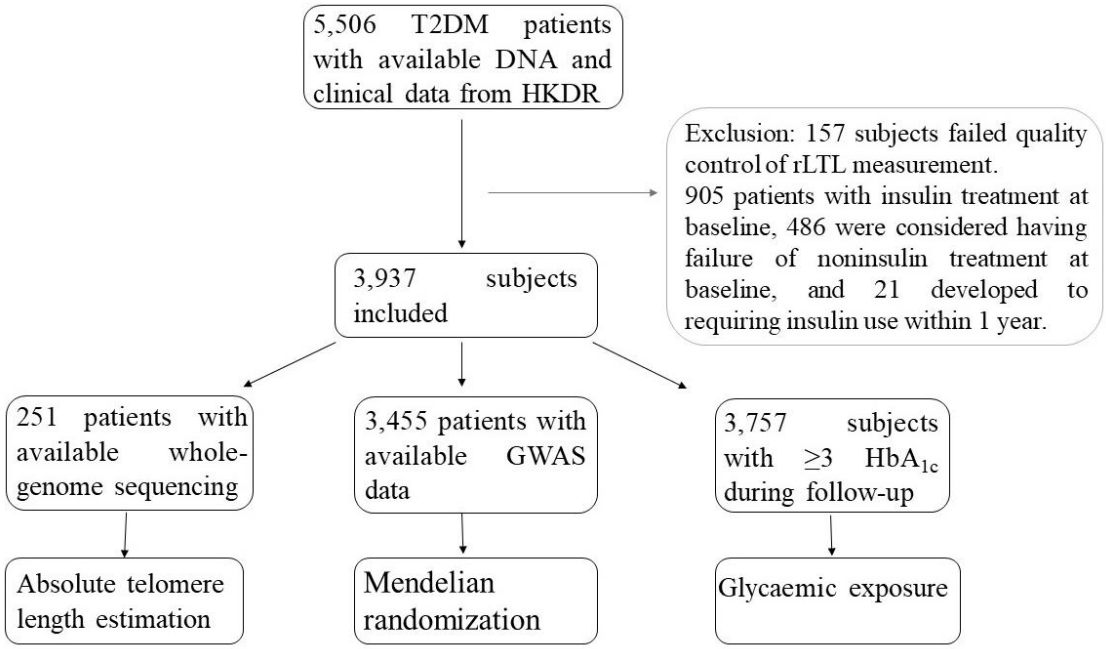


Figure S4. Flow diagram of patient selection

Abbreviation: T2DM, type 2 diabetes; HKDR, Hong Kong Diabetes Register; rLTL, relative leukocyte telomere length; GWAS, Genome-Wide Association Study.

Reference for supplementary

1. World Health Organization. The Asian-Pacific perspective: redefining obesity and its treatment, WHO Western Pacific Region, Geneva, Switzerland. 2000.