

## APPENDIX: Supplementary Materials

Figure S1. Procedure to select eligible study participants

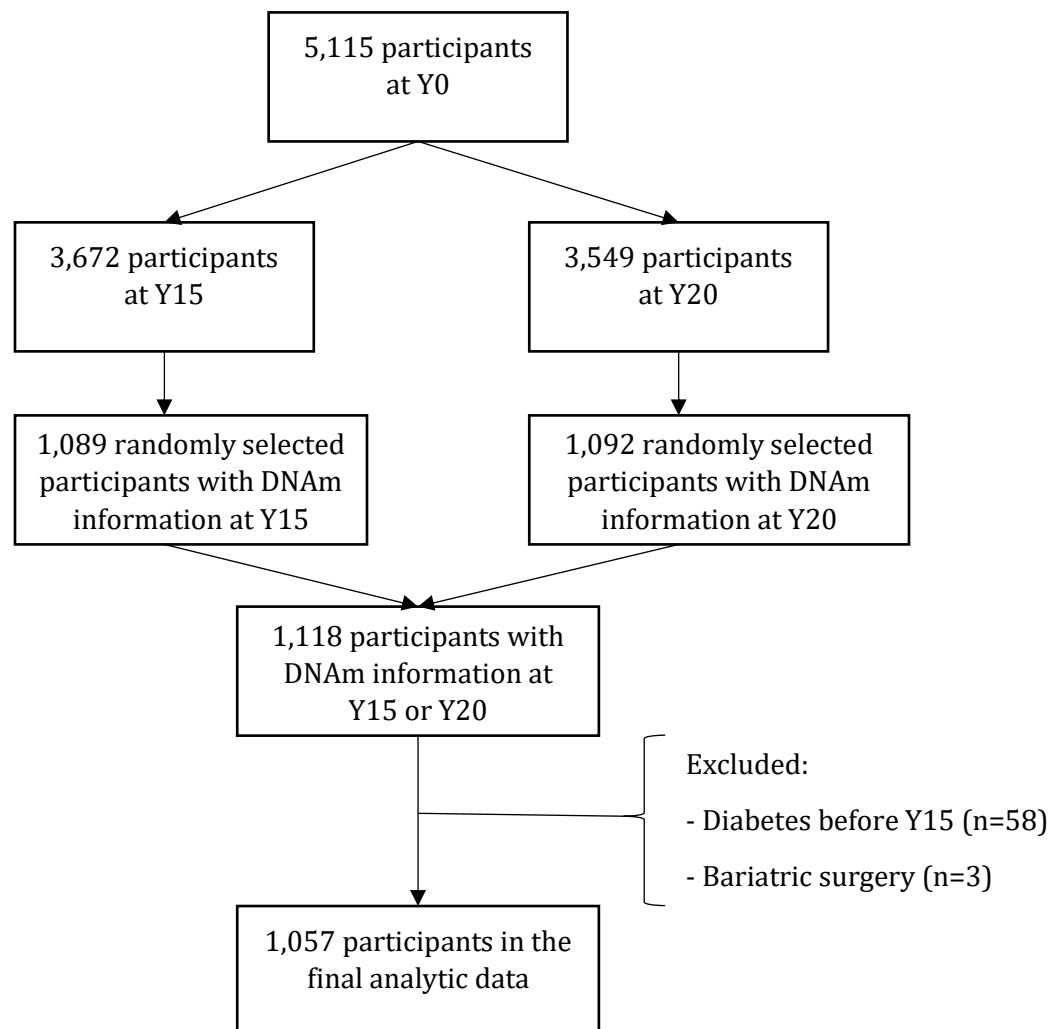


Table S1. Correlations between epigenetic age measurements and chronological age

	R2	p
Y15 GrimAge and chronological age	0.47	<.001
Y15 GrimAA and chronological age	0.00	1.00
Y20 GrimAge and chronological age	0.46	<.001
Y20 GrimAA and chronological age	0.00	1.00

Table S2. Race-stratified analysis for associations between GrimAge measurements at Y15-Y20 and incidence of hyperglycemia (diabetes or prediabetes) during Y15-Y25

	Normal weight at Y15	Overweight at Y15	With obesity at Y15	P-interaction†
	(BMI <25)	(BMI 25-30)	(BMI ≥30)	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	
<i>Black (N=423)</i>	N=98	N=150	N=175	
GrimAge	1.04 (0.98-1.11)	1.00 (0.95-1.06)	1.04 (0.98-1.10)	0.85
GrimAA	0.98 (0.91-1.05)	1.00 (0.93-1.07)	0.96 (0.88-1.05)	0.58
Positive GrimAA	1.41 (0.74-2.70)	0.80 (0.45-1.45)	0.75 (0.42-1.37)	0.23
Positive 5yr GrimAA	0.72 (0.25-2.02)	0.93 (0.44-1.96)	2.11 (0.95-4.69)	0.08
<i>White (N=634)</i>	N=247	N=244	N=143	
GrimAge	<b>1.09 (1.03-1.15)**</b>	<b>1.05 (1.01-1.10)*</b>	1.06 (0.99-1.15)	<0.01
GrimAA	1.06 (0.97-1.16)	1.06 (0.98-1.13)	1.01 (0.91-1.12)	0.57
Positive GrimAA	<b>3.04 (1.34-6.86)**</b>	1.07 (0.64-1.80)	1.61 (0.81-3.21)	<0.01
Positive 5yr GrimAA	1.45 (0.75-2.80)	1.17 (0.67-2.04)	1.89 (0.82-4.33)	<0.01

Models adjusted for sex, education, smoking status, physical activity, alcohol drinking, and field center; \*p<0.05; \*\*p<0.01. † P-values for interaction between GrimAge measurements and obesity status.

Table S3. Sex-stratified analysis for associations between GrimAge measurements at Y15-Y20 and incidence of hyperglycemia (diabetes or prediabetes) during Y15-Y25

	Normal weight at Y15	Overweight at Y15	With obesity at Y15	p-interaction†
	(BMI <25)	(BMI 25-30)	(BMI ≥30)	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	
<i>Male (N=534)</i>	N=141	N=243	N=150	
GrimAge	1.05 (0.98-1.12)	1.02 (0.98-1.06)	1.00 (0.93-1.06)	0.35
GrimAA	0.99 (0.90-1.07)	1.02 (0.96-1.09)	0.93 (0.85-1.02)	0.4
Positive GrimAA	1.67 (0.80-3.47)	0.90 (0.58-1.41)	1.10 (0.56-2.14)	0.47
Positive 5yr GrimAA	0.79 (0.35-1.74)	0.79 (0.44-1.42)	1.96 (0.80-4.81)	0.17
<i>Female (N=523)</i>	N=204	N=151	N=168	
GrimAge	1.07 (1.02-1.13)	1.06 (1.00-1.13)	<b>1.09 (1.03-1.14)**</b>	0.64
GrimAA	1.05 (0.98-1.12)	1.06 (0.95-1.16)	1.01 (0.94-1.09)	0.89
Positive GrimAA	2.67 (1.38-5.18)	1.28 (0.58-2.85)	1.01 (0.59-1.74)	0.09
Positive 5yr GrimAA	1.66 (0.97-2.86)	1.57 (0.75-3.29)	<b>2.17 (1.31-3.58)**</b>	0.58

Models adjusted for sex, education, smoking status, physical activity, alcohol drinking, and field center; \*p<0.05; \*\*p<0.01. † P-values for interaction between GrimAge measurements and obesity status.

Table S4. Associations between PhenoAge measurements at Y15-Y20 and incident T2D during Y15-Y25, by BMI status at Y15

	Normal weight at Y15 (BMI <25, N=345)	Overweight at Y15 (BMI 25-30, N=394)	With obesity at Y15 (BMI ≥30, N=318)	P-interaction
	OR (95% CI)	OR (95% CI)	OR (95% CI)	
<i>Model 1: diabetes vs. prediabetes and normal glucose</i>				
PhenoAge	1.02 (0.93-1.13)	0.98 (0.93-1.04)	1.03 (0.99-1.07)	0.95
PhenoAA	1.03 (0.93-1.13)	0.98 (0.93-1.05)	1.03 (0.98-1.08)	0.81
Positive PhenoAA	1.66 (0.56-4.90)	0.94 (0.48-1.83)	1.52 (0.90-2.55)	0.68
Positive 5yr PhenoAA	1.10 (0.35-3.40)	0.37 (0.14-1.00)	1.32 (0.70-2.50)	0.16
<i>Model 2: diabetes vs. normal glucose (prediabetes excluded)</i>				
PhenoAge	1.02 (0.93-1.13)	0.96 (0.90-1.02)	1.04 (0.99-1.09)	0.55
PhenoAA	1.02 (0.93-1.12)	0.96 (0.89-1.03)	1.04 (0.99-1.09)	0.40
Positive PhenoAA	1.70 (0.55-5.30)	0.75 (0.36-1.56)	<b>1.90 (1.06-3.42)*</b>	0.33
Positive 5yr PhenoAA	1.04 (0.32-3.37)	<b>0.24 (0.08-0.76) *</b>	2.05 (0.96-4.37)	0.12
<i>Model 3: hyperglycemia (diabetes or prediabetes) vs. normal glucose</i>				
PhenoAge	1.02 (0.99-1.05)	1.00 (0.97-1.02)	1.02 (0.99-1.05)	0.68
PhenoAA	1.02 (0.98-1.05)	1.00 (0.97-1.03)	1.02 (0.99-1.06)	0.70
Positive PhenoAA	1.34 (0.89-2.03)	0.98 (0.68-1.40)	1.27 (0.85-1.90)	0.86
Positive 5yr PhenoAA	<b>1.91 (1.13-3.22)*</b>	0.67 (0.43-1.04)	<b>1.84 (1.11-3.06)*</b>	0.68

Models adjusted for age (for models with PhenoAge), race, sex, education, smoking status, physical activity, alcohol drinking, and field center;

\*p<0.05; \*\*p<0.01; \*\*\*p<0.001.

Table S5. Associations between PhenoAge measurements at Y15-Y20 and incident T2D during Y15-Y30, by BMI status at Y15

	Normal weight at Y15 (BMI <25, N=315)	Overweight at Y15 (BMI 25-30, N=365)	With obesity at Y15 (BMI ≥30, N=287)	P-interaction
	OR (95% CI)	OR (95% CI)	OR (95% CI)	
<i>Model 1: diabetes vs. prediabetes and normal glucose</i>				
PhenoAge	1.04 (0.95-1.13)	1.01 (0.96-1.06)	<b>1.04 (1.00-1.08)*</b>	0.90
PhenoAA	1.04 (0.95-1.14)	1.01 (0.96-1.06)	1.04 (1.00-1.09)	0.71
Positive PhenoAA	1.00 (0.36-2.76)	1.17 (0.64-2.12)	<b>1.62 (1.02-2.57)*</b>	0.45
Positive 5yr PhenoAA	1.17 (0.39-3.52)	0.64 (0.28-1.47)	1.44 (0.80-2.58)	0.45
<i>Model 2: diabetes vs. normal glucose (prediabetes excluded)</i>				
PhenoAge	1.06 (0.96-1.18)	0.97 (0.91-1.04)	1.03 (0.98-1.08)	0.94
PhenoAA	1.04 (0.95-1.14)	1.02 (0.96-1.08)	1.03 (0.99-1.08)	0.89
Positive PhenoAA	1.01 (0.36-2.84)	1.11 (0.59-2.07)	1.58 (0.93-2.66)	0.54
Positive 5yr PhenoAA	1.32 (0.43-4.07)	0.63 (0.27-1.50)	1.48 (0.78-2.81)	0.48
<i>Model 3: hyperglycemia (diabetes or prediabetes) vs. normal glucose</i>				
PhenoAge	1.02 (0.99-1.05)	1.01 (0.98-1.04)	1.01 (0.98-1.04)	0.20
PhenoAA	1.02 (0.99-1.06)	1.01 (0.98-1.04)	1.00 (0.97-1.04)	0.42
Positive PhenoAA	1.21 (0.84-1.75)	0.97 (0.68-1.39)	1.06 (0.72-1.56)	0.65
Positive 5yr PhenoAA	<b>1.67 (1.15-2.42)**</b>	1.07 (0.69-1.64)	1.22 (0.75-2.00)	0.40

Models adjusted for age (for models with PhenoAge), race, sex, education, smoking status, physical activity, alcohol drinking, and field center;

\*p<0.05; \*\*p<0.01; \*\*\*p<0.001.

Table S6. Comparison of area under the curve (AUC) between chronological age and epigenetic age measurements from receiver operating characteristics (ROC) curve analysis

Chronological or Epigenetic age measurements	T2D during Y15-Y25, AUC (95% CI)			T2D during Y15-Y30, AUC (95% CI)		
	T2D	T2D, excluding prediabetes	Hyperglycemia (diabetes or prediabetes)	T2D	T2D, excluding prediabetes	Hyperglycemia (diabetes or prediabetes)
<i>Age measures at Y15</i>						
Chronological age at Y15	0.55 (0.48 - 0.61)	0.58 (0.51 - 0.64)	0.58 (0.54 - 0.61)	0.50 (0.44 - 0.56)	0.52 (0.46 - 0.58)	0.55 (0.51 - 0.58)
GrimAge at Y15	0.61 (0.55 - 0.68)	0.66 (0.59 - 0.72)	0.62 (0.58 - 0.65)	0.58 (0.53 - 0.64)	0.60 (0.55 - 0.66)	0.57 (0.54 - 0.61)
GrimAA at Y15	0.62 (0.56 - 0.68)	0.66 (0.60 - 0.71)	0.60 (0.57 - 0.64)	0.61 (0.56 - 0.66)	0.63 (0.57 - 0.68)	0.57 (0.53 - 0.60)
PhenoAge at Y15	0.57 (0.51 - 0.63)	0.59 (0.53 - 0.65)	0.56 (0.52 - 0.59)	0.58 (0.53 - 0.64)	0.59 (0.54 - 0.65)	0.55 (0.51 - 0.58)
PhenoAA at Y15	0.57 (0.51 - 0.63)	0.57 (0.51 - 0.64)	0.53 (0.49 - 0.56)	0.59 (0.54 - 0.65)	0.59 (0.54 - 0.65)	0.53 (0.49 - 0.56)
<i>Age measures at Y20</i>						
Chronological age at Y20	0.55 (0.48 - 0.62)	0.58 (0.51 - 0.65)	0.57 (0.54 - 0.61)	0.50 (0.44 - 0.56)	0.52 (0.45 - 0.58)	0.55 (0.51 - 0.59)
GrimAge at Y20	0.61 (0.54 - 0.68)	0.66 (0.59 - 0.72)	0.62 (0.58 - 0.66)	0.59 (0.53 - 0.65)	0.62 (0.56 - 0.68)	0.60 (0.56 - 0.64)
GrimAA at Y20	0.61 (0.54 - 0.67)	0.64 (0.58 - 0.71)	0.60 (0.57 - 0.64)	0.60 (0.54 - 0.66)	0.63 (0.57 - 0.69)	0.59 (0.55 - 0.63)
PhenoAge at Y20	0.57 (0.50 - 0.64)	0.60 (0.53 - 0.67)	0.57 (0.54 - 0.61)	0.58 (0.51 - 0.64)	0.59 (0.53 - 0.66)	0.57 (0.53 - 0.60)
PhenoAA at Y20	0.55 (0.48 - 0.62)	0.57 (0.49 - 0.64)	0.55 (0.51 - 0.58)	0.58 (0.52 - 0.65)	0.59 (0.53 - 0.66)	0.55 (0.51 - 0.59)