Methods and Applications

AI-Based Hematological Age Predictors and the Association Between Biological Age Acceleration and Type 2 Diabetes Mellitus — Chongqing Municipality, China, 2015–2021

Zhe Yin[1,2,&]; Yingnan Song[3,&]; Junhui Zhang[4,&]; Qiaoyun Dai[1,2]; Xinyuan Zhang[1,2]; Xueying Yang[1,2]; Na Nie[4]; Cuixia Chen[1,2]; Zongfu Cao[1,#]; Xu Ma[2,3,#]

ABSTRACT

Introduction: Biological age (BA) can represent the actual state of human aging more accurately than chronological age (CA).

Methods: Using hematological data from 112,925 participants in southwestern China, collected between 2015 and 2021, this study constructed BA predictors using 7 machine learning (ML) methods (tailored separately for male and female populations). This study then analyzed the association between BA acceleration and type 2 diabetes mellitus (T2DM) within this data using logistic regression. Additionally, it examined the impact of glycemic control on BA in individuals with diabetes.

Results: Among all ML models, deep neural networks (DNN) delivered the best performance in male [mean absolute error (MAE)=6.89, r=0.75] and female subsets (MAE=6.86, r=0.74). BA acceleration showed positive correlations with T2DM in both male [odds ratio (*OR*): 2.22, 95% confidence interval (*CI*): 1.77–2.77] and female subsets (*OR*: 3.10, 95% *CI*: 2.16–4.46), while BA deceleration showed negative correlations in both male (*OR*: 0.32, 95% *CI*: 0.27–0.39) and female subsets (*OR*: 0.42, 95% *CI*: 0.33–0.53). Individuals with diabetes with normal fasting glucose had significantly lower BAs than those with impaired fasting glucose in all CA groups except for patients older than 80.

Discussion: Artificial intelligence (AI)-based hematological BA predictors show promise as advanced tools for assessing aging in epidemiological studies. Implementing AI-based BA predictors in public health initiatives could facilitate proactive aging management and disease prevention.

Aging is a process characterized by the gradual decline of various molecular functions and the progressive accumulation of senescent cells, increasing the risk of diseases such as neurodegenerative diseases (*1*), cerebral ischemia (*2*), cancer (*3*), and vasculitis (*4*). Research has evolved the definition of aging from a simple increase in chronological age to a systematic assessment of overall physiological function. Different bodily systems and organs may exhibit varying aging rates, suggesting the presence of multiple "clocks" (*5*). Hematological features have been employed to develop biological age (BA) prediction models in populations from the USA (*6*), Singapore (*7*), the Republic of Korea (*8*,*9*), Canada (*9*), and eastern Europe (*9*). BA serves as a valuable tool for identifying biomarkers and exploring risk and protective factors associated with aging. Machine learning (ML) techniques, particularly deep learning, are playing an increasingly important role in accurately predicting BA. This advancement not only enhances our understanding of healthy aging but also provides the public health sector with a powerful tool. Deep learning, an important ML method used to predict BA since 2016 (*6*), leverages deep neural networks (DNN) to improve model interpretability through enhanced nonlinear fitting, learning, and generalization abilities (*10*).

This study established and evaluated hematological BA prediction models in a large Chinese population. 7 ML methods based on 20 blood test features were used. Further analysis showed an association between BA acceleration and T2DM. The analysis also showed that controlling fasting blood glucose within normal levels may decrease BA. The study further revealed the association between BA and chronological age (CA), indicating that even among individuals with the same CA, there can be significant differences in BA, which often reflect variations in health status among individuals.

METHODS

Data Collection and Preprocessing

29 blood test features from 145,645 individuals were collected from the physical examination data center of the First Affiliated Hospital of Chongqing Medical University between 2015 and 2021. Supplementary Table S1 (available at https://weekly.chinacdc.cn/) provides a comprehensive overview of the participants' demographic profiles. This dataset includes five categories: blood routine examination, cardiovascular efficiency, diabetes mellitus, liver function, and renal function (Supplementary Table S2, available at https://weekly.chinacdc.cn/). Outliers for each variable in the dataset were removed using the quartile method (*11*). After removing features with multicollinearity, the remaining features were normalized to a range of 0 to 1. Multicollinearity can impact the individual effects of each explanatory variable, as well as model stability and generalization error. To ascertain multicollinearity within the dataset of 29 features, the variance inflation factor (VIF) was calculated. A feature was considered to exhibit multicollinearity if its VIF exceeded a threshold of 10.

BA Predictor Models

The datasets for male and female participants were randomly split into training, validation, and testing datasets at a ratio of 7∶2∶1. Seven ML methods, namely, DNN, support vector regression (SVR), stochastic gradient descent (SGD), kernel ridge regression (KRR), Least Absolute Shrinkage and Selection Operator (LASSO), K-nearest neighbors (KNN), and gradient boosting for regression (GBR), were used to build BA prediction models, with each model being optimized through parameter adjustment. To assess the performance of each model, Pearson's correlation coefficient (r) and the mean absolute error (MAE) were calculated. Additionally, permutation feature importance (PFI) was used to measure the contribution of features in DNN models. This process involved 100 permutations for each feature, and the average decrease in the coefficient of determination (R^2) was calculated before and after the permutation. In summary, the study comprehensively analyzed features of blood tests to develop and evaluate BA prediction models by applying various ML methods.

Association Analysis between BA Acceleration and T2DM

Participants with a difference between BA and CA greater than 7 years were classified as the BA acceleration group, while those with a difference less than −7 years comprised the BA deceleration group. The remaining participants constituted the control group. The T2DM status of each participant was self-reported based on previous medical history. Logistic regression, with BMI and CA as covariates, was used to analyze the association between BA acceleration and T2DM. Participants with T2DM were further divided into two groups based on glycemic control: those with impaired fasting glucose (IFG) and those with normal fasting glucose (NFG) after treatment. All individuals were categorized into six CA groups. The Kruskal-Wallis H test was used to analyze differences in BA-CA across the three groups (non-diabetic, IFG, and NFG) for each CA group in both male and female participants.

Statistical Analysis

SPSS (version 25.0; IBM Corporation, Armonk, NY, USA), R software (version 3.6.1; R Foundation, Vienna, Austria), Python (version 3.8.3; maintained by the Python Software Foundation, Chicago, IL, USA), and TensorFlow software (version 2.7.0; developed by Google Brain Team, Mountain View, CA, USA) were used to perform the analyses.

RESULTS

Dataset Preprocessing and Subsets Description

In this study, CA ranged from 11.44 to 99.82, with a detailed distribution shown in Supplementary Figure S1 (available at https://weekly.chinacdc.cn/). After outlier detection using the quartile method, 32,720 of 145,645 individuals were removed. Due to multicollinearity and strong correlations with other features, nine features were excluded (Supplementary Figure S2 and Supplementary Table S2, available at https://weekly.chinacdc.cn/). Figure 1 presents the process flowchart and sample size for each subset.

Hematological BA Models & Evaluation

Seven optimal BA prediction models were constructed using ML methods. Among these, the DNN model showed the highest coefficient and lowest mean absolute error (MAE) across the training, validation, and testing datasets (Supplementary Table S3, available at https://weekly.chinacdc.cn/). Subsequently, the DNN BA predictors were used to

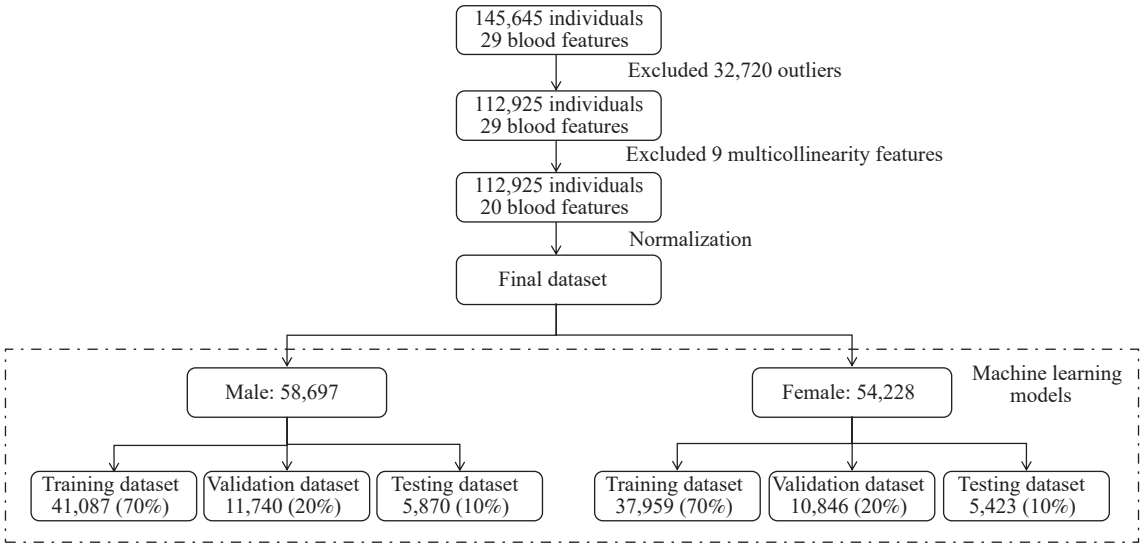

FIGURE 1. Optimized workflow for data processing and management.

predict hematological BA for both male and female subsets. Notably, strong correlations between hematological BA and CA were observed in the male and female training, validation, and testing datasets (Figure 2).

Feature Importance Analysis

The average decrease in model performance was calculated by randomly permuting features. The differences in the coefficients of determination (R^2) of features before and after random permutation were calculated as the feature importance values (Supplementary Figure S3, available at https://weekly.chinacdc.cn/). The top five important features in the BA prediction model in male subjects were albumin, fasting blood glucose, platelet hematocrit, mean corpuscular volume, and serum total cholesterol (Supplementary Figure S3A), whereas the top five features in the BA prediction model in female subjects were albumin, fasting blood glucose, serum total cholesterol, triglycerides, and urea (Supplementary Figure S3B). In both models, albumin and fasting blood glucose ranked first and second in terms of importance. Moreover, albumin was twice as important in the male model as in the female model, with almost no difference in fasting blood glucose.

Association between BA and T2DM

A total of 1,362 individuals with diabetes and 100,818 individuals without diabetes were included in this study to investigate the risk of BA acceleration or deceleration on diabetes incidence. Using logistic regression analysis, BA acceleration showed positive correlations with T2DM in both male [odds ratio (*OR*): 2.22, 95% confidence interval (*CI*): 1.77–2.77] and female subjects (*OR*: 3.10, 95% *CI*: 2.16–4.46), while BA deceleration showed negative correlations with T2DM in both male (*OR*: 0.32, 95% *CI*: 0.27–0.39) and female subjects (*OR*: 0.42, 95% *CI*: 0.33–0.53) (Table 1).

To observe whether glycemic control affected hematological BA in six CA groups, 1,362 diabetic subjects were divided into IFG and NFG groups (Supplementary Table S4, available at https://weekly.chinacdc.cn/). Using the Kruskal–Wallis H test, NFG diabetic subjects had significantly lower BAs than IFG diabetic subjects in all CA groups except those older than 80 years. Concurrently, there were no significant BA differences between NFG diabetic and nondiabetic subjects, except for individuals younger than 40 years (Figure 3).

DISCUSSION

In this study, sex-specific hematological BA prediction models constructed using the DNN algorithm showed good performance in a southwestern Chinese population. DNN outperformed six other ML methods, yielding the smallest MAE and largest correlation coefficient. This study also showed that hematological BA acceleration may be a strong risk factor for T2DM in males and females, while BA deceleration may be protective. Controlling fasting blood glucose within normal levels in those with T2DM may decrease hematological BA. This

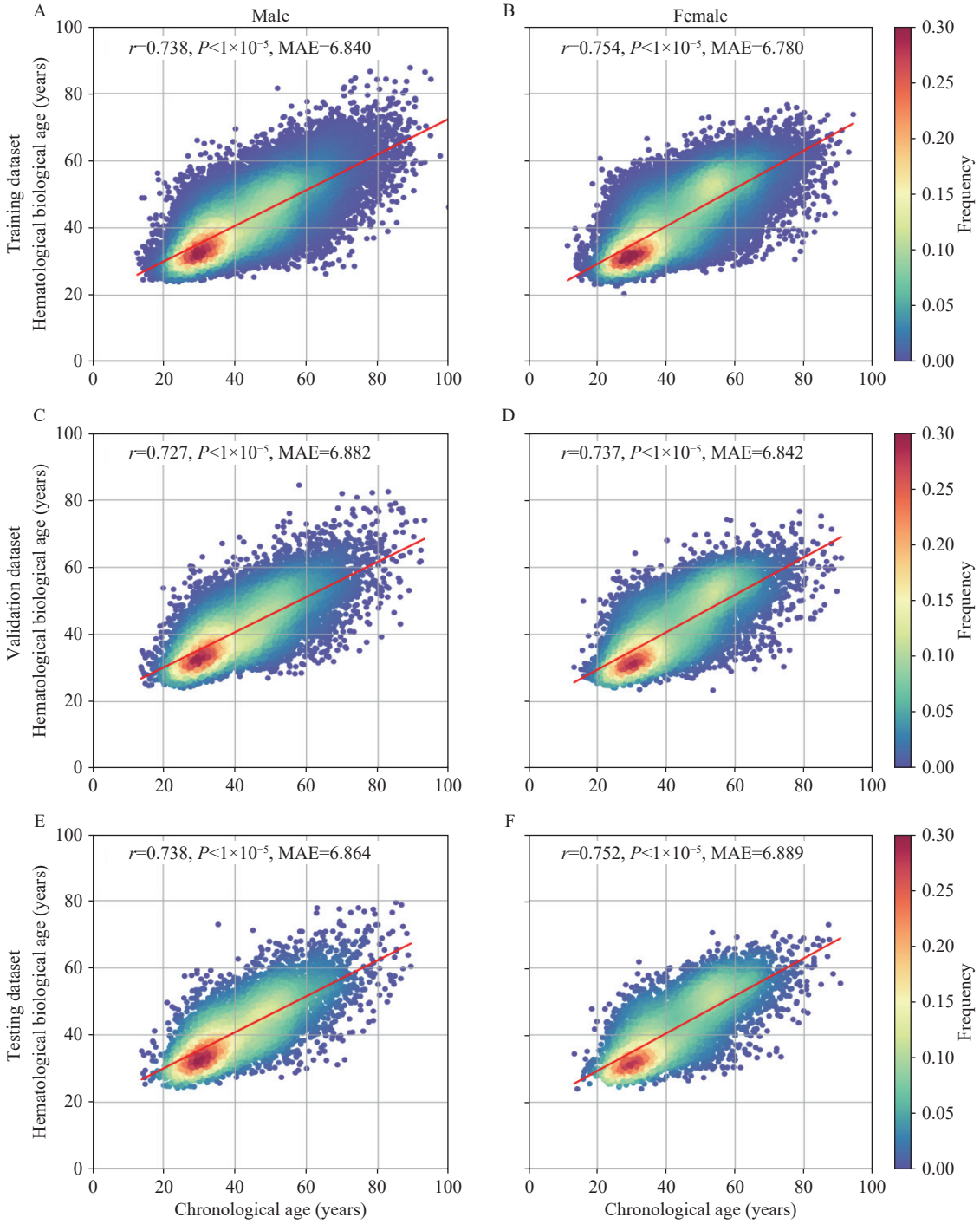

FIGURE 2. Correlations between hematological biological age and chronological age based on deep neural network models in the training, validation, and testing datasets. (A) Training dataset — Male; (B) Training dataset — Female; (C) Validation dataset — Male; (D) Validation dataset — Female; (E) Testing dataset — Male; (F) Testing dataset — Female.
Note: The colors represent the Gaussian kernel density estimation value.

observation highlights the importance of leveraging BA prediction tools to monitor the biological aging process in middle-aged and older adults (*12*), thereby informing personalized health management strategies for those at heightened risk for T2DM. Identifying individuals with a high risk of T2DM enables prompt actions to advocate for lifestyle changes, including a balanced diet, increased physical activity, and stress management. These proactive measures not only prevent the onset of T2DM but also improve the overall health of at-risk populations, halting disease progression before stages requiring intensive medical

TABLE 1. Gender differences in the impact of biological age acceleration and deceleration, body mass index, and chronological age on type 2 diabetes mellitus risk: estimation of odds ratios.

Factors	Male			Female		
	Coefficients	*ORs (95% CI)*	*P*	Coefficients	*ORs (95% CI)*	*P*
Body mass index	0.05	1.05 (1.03–1.06)	<0.001	0.03	1.03 (1.01–1.04)	0.006
Chronological age	0.11	1.12 (1.11–1.12)	<0.001	0.14	1.14 (1.13–1.16)	<0.001
Accelerate	0.80*	2.22 (1.77–2.77)*	<0.001	1.13*	3.10 (2.16–4.46)*	<0.001
Decelerate	−1.13*	0.32 (0.27–0.39)*	<0.001	−0.87*	0.42 (0.33–0.53)*	<0.001

Abbreviation: *OR*=odds ratio. *CI*=confidence interval.
* indicates that the acceleration of biological age is positively correlated with type 2 diabetes mellitus in both male and female subjects, while the deceleration of biological age is negatively correlated with type 2 diabetes mellitus.

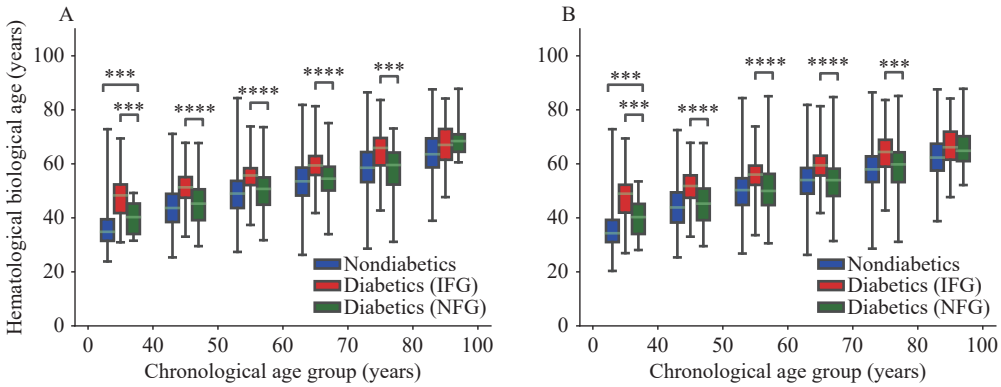

FIGURE 3. Boxplot of biological age in different age groups by gender for diabetic and non-diabetic individuals (A) Male; (B) Female.
Note: The significance levels were Bonferroni corrected.
Abbreviation: IFG=impaired fasting glucose; NFG=normal fasting glucose.
*** means $P \leq 0.001$;
**** means $P \leq 0.0001$.

care and diminishing healthcare costs.

Because information on the included features is widely available and easily obtained from routine hematological examinations, the BA prediction models may be widely applicable for assessing BA acceleration status, especially in retrospective cohort studies. Therefore, large, multicenter cohorts based on clinical or physical examination data could be established to facilitate extensive studies on the causes and adverse outcomes of accelerated aging. For example, Lu Chen et al. demonstrated an association between BA acceleration and the risk of cardiovascular events and all-cause mortality; specifically, integrating BA acceleration into mortality prediction increased Harrell's C-index from 0.813 to 0.821 (*13*).

This study's BA prediction models demonstrate significant potential for large-scale population health research, reshaping public health strategies by identifying individuals at risk of accelerated aging and elevated disease susceptibility. This precision fosters personalized preventive measures and targeted therapies. It has been reported that a majority of hematological markers are associated with both gender and age (*14*). Tracking hematological markers facilitates the mapping of aging patterns across diverse populations, informing strategic resource allocation and the design of tailored health preservation initiatives. However, this study was cross-sectional, and future cohort studies will assess the associations between hematological BA acceleration and other diseases.

In conclusion, AI-based hematological BA predictors using DNNs were established and demonstrated good performance in a large Chinese population, suggesting that they may be promising methods for assessing accelerated BA status in epidemiological studies of aging.

Conflicts of interest: No conflicts of interest.

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Corresponding authors: Zongfu Cao, caozongfu@egene.org.cn; Xu Ma, maxu_ky@nrifp.org.cn.

[1] National Human Genetic Resources Center, National Research Institute for Family Planning, Beijing, China; [2] National Human Genetic Resources Sharing Service Platform, National Research Institute for Family Planning, Beijing, China; [3] Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; [4] The First Affiliated Hospital of Chongqing Medical University, Chongqing, China.
& Joint first authors.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Demographic characteristics of study participants.

Year	2016	2017	2018	2019	2020	2021
Sample size	15,689	16,937	21,521	26,066	16,021	16,691
Age, median (SD)	40.75 (12.85)	38.87 (12.73)	39.32 (13.36)	34.56 (13.07)	40.19 (13.65)	37.90 (13.60)
Age, range	14.42–99.82	13.42–94.78	12.76–90.00	13.38–93.15	13.34–93.42	11.44–97.37
Sex						
Female (%)	6,644 (42.35)	7,812 (46.12)	10,092 (46.89)	12,492 (47.92)	8,187 (51.10)	9,001 (53.93)
Male (%)	9,045 (57.65)	9,125 (53.88)	11,429 (53.11)	13,574 (52.08)	7,834 (48.90)	7,690 (46.07)
BMI (SD)	23.14 (5.19)	24.26 (4.00)	24.00 (6.51)	22.83 (3.37)	22.83 (3.61)	22.94 (3.66)

Note: The number of individuals undergoing health examinations in 2015 was 475, and due to the smaller sample size, it was combined with that of 2016.
Abbreviation: SD=standard deviation; BMI=body mass index.

SUPPLEMENTARY TABLE S2. The information of twenty-nine features and correlation between features and chronological age.

Abbreviation	Full name	Class	Pearson correlation	*P*	VIF
ALB	Albumin	Liver function	−0.37	0	21.7
FBG	Fasting blood glucose	Diabetes mellitus	0.34	0	1.13
TC	Serum total cholesterol	Cardiovascular efficiency	0.29	0	17.0
LDL	Low density lipoprotein	Cardiovascular efficiency	0.26	0	13.7
Urea	Urea	Renal function	0.25	0	1.15
MCV	Mean corpuscular volume	Blood routine examination	0.24	0	642
PCT	Platelet hematocrit	Blood routine examination	−0.22	0	27.1
PLT	Platelet count	Blood routine examination	−0.22	0	39.7
TP	Total protein	Liver function	−0.19	0	19.6
RBC	Red blood cell count	Blood routine examination	−0.18	0	425
AG	ALB/GLB	Liver function	−0.17	0	22.8
TG	Triglyceride	Cardiovascular efficiency	0.17	0	2.26
MCH	Mean corpuscular hemoglobin	Blood routine examination	0.14	0	845
MCHC	Mean corpuscular hemoglobin concentration	Blood routine examination	−0.13	0	229
HGB	Hemoglobin	Diabetes mellitus	−0.11	5.55×10^{-294}	1,094
HCT	Red blood cell specific volume	Blood routine examination	−0.08	1.01×10^{-176}	1,206
DBIL	Direct bilirubin	Liver function	−0.08	3.46×10^{-165}	4.20
MPV	Mean platelet volume	Blood routine examination	0.08	2.95×10^{-154}	115
P-LCR	Platelet-larger cell ratio	Blood routine examination	0.08	8.62×10^{-146}	114
WBC	White blood cell count	Blood routine examination	−0.07	1.24×10^{-128}	1.45
LY%	Percentage of lymphocyte	Blood routine examination	−0.06	6.90×10^{-102}	13.4
GLB	Globulin	Liver function	0.06	4.53×10^{-84}	.
MONO%	Percentage of monocytes	Blood routine examination	0.05	5.62×10^{-61}	1.54
HDL	High-density lipoprotein cholesterol	Cardiovascular efficiency	0.05	3.86×10^{-54}	3.68
TBIL	Total bilirubin	Liver function	0.03	2.73×10^{-27}	3.76
NEU%	Percentage of granulocyte	Blood routine examination	0.03	9.93×10^{-27}	13.8
Cr	Creatinine	Renal function	0.03	1.74×10^{-17}	1.79
PDW	Platelet distribution width	Blood routine examination	0.02	7.83×10^{-16}	1.17
ALT	Alanine aminotransferase	Liver function	−0.01	0.003	1.37

Note: "." note the VIF value is excessively large, the tool can't be able to display it properly. After performing multicollinearity diagnosis, HCT, RBC, LDL, AG, PCT, P_LCR, MCH, NEU_PCT and GLB were excluded.
Abbreviation: VIF=variance inflation factor.

SUPPLEMENTARY TABLE S3. Performance comparison of seven machine learning methods by gender in each dataset based on MAE and *r*.

Model	Training dataset				Validation dataset				Testing dataset			
	Male		Female		Male		Female		Male		Female	
	MAE	*r*	MAE	*r*	MAE	*r*	MAE	*r*	MAE	*r*	MAE	*r*
DNN*	6.84	0.74	6.78	0.75	6.88	0.73	6.84	0.74	6.89	0.75	6.86	0.74
SVR	6.92	0.73	6.94	0.74	6.99	0.72	7.00	0.73	7.11	0.73	6.98	0.73
SGD	7.50	0.69	7.55	0.70	7.45	0.69	7.50	0.69	7.59	0.70	7.49	0.69
KRR	7.86	0.65	7.64	0.69	7.82	0.65	7.60	0.68	7.68	0.69	7.88	0.65
LASSO	7.85	0.67	7.92	0.69	7.79	0.67	7.80	0.68	7.97	0.69	7.82	0.68
KNN	7.62	0.71	7.52	0.72	7.73	0.69	7.55	0.70	7.72	0.70	7.70	0.70
GBR	7.10	0.72	7.12	0.74	7.20	0.71	7.19	0.72	7.26	0.73	7.18	0.72

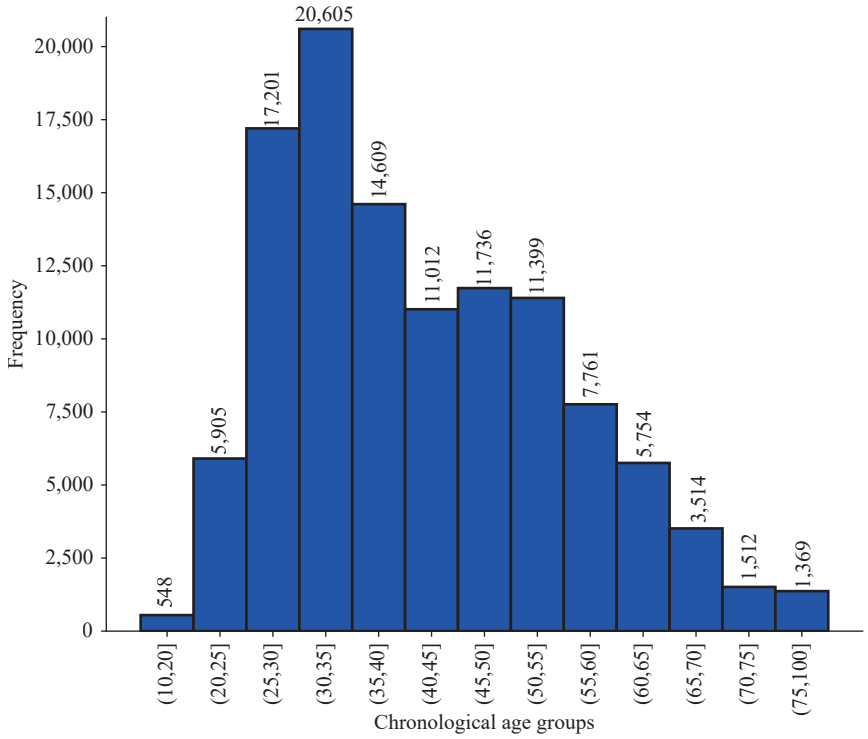
Abbreviation: MAE=mean absolute error; *r*=pearson's correlation coefficient; DNN=deep neural networks; SVR=support vector regression; SGD=stochastic gradient descent; KRR=kernel ridge regression; LASSO=Least Absolute Shrinkage and Selection Operator; KNN=K-nearest neighbors; GBR=gradient boosting for regression.

* highlights the superior performance of the DNN model in comparison to other models across the training, validation, and testing datasets.

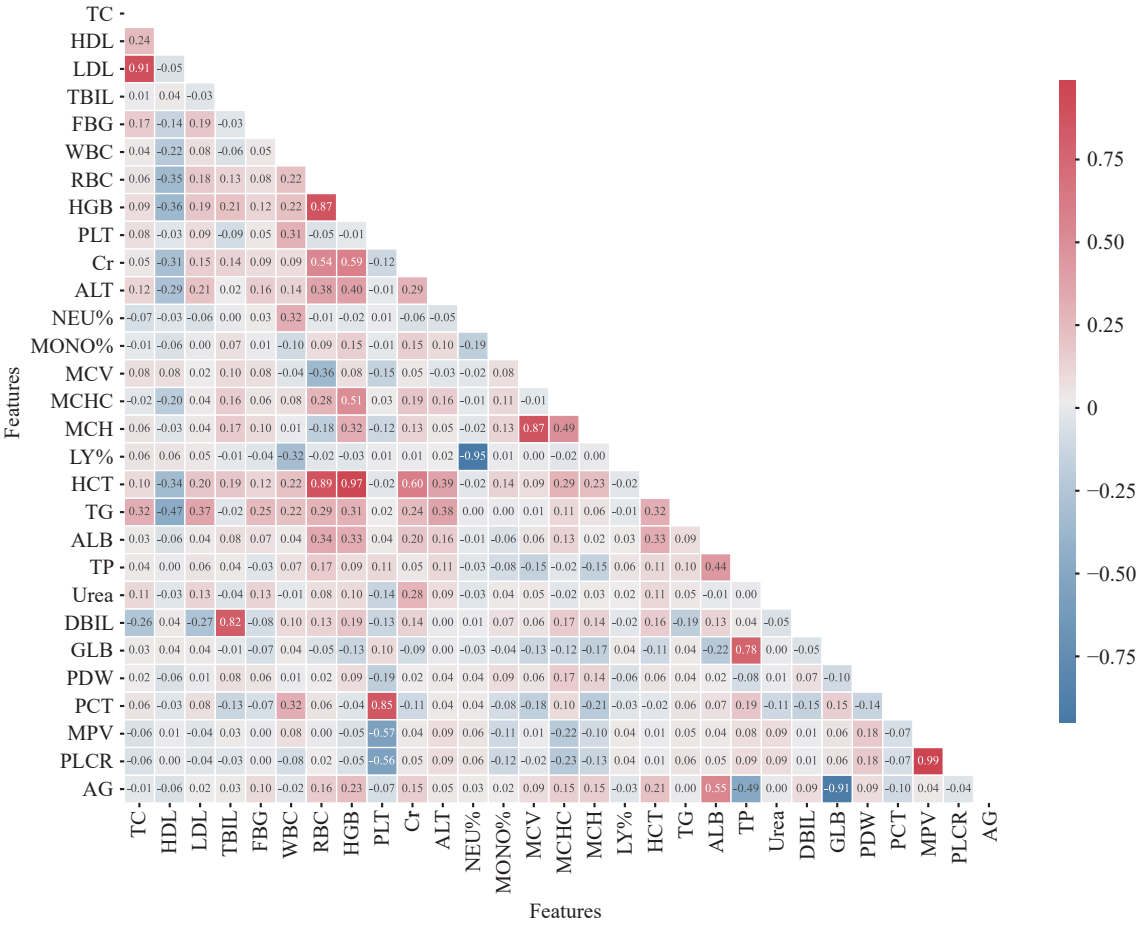
SUPPLEMENTARY TABLE S4. Statistics on the number of male and female individuals in different age ranges for each group.

Groups	Nondiabetics		Diabetics IFG		Diabetics NFG	
	Male	Female	Male	Female	Male	Female
(10,40]	28,668	24,094	29	5	14	12
(40,50]	11,347	9,005	123	17	40	6
(50,60]	8,400	8,680	215	92	92	51
(60,70]	3,941	4,262	167	117	62	62
(70,80]	1,013	966	68	54	31	38
(80,100]	279	163	30	13	12	12
Sum	53,648	47,170	632	298	251	181

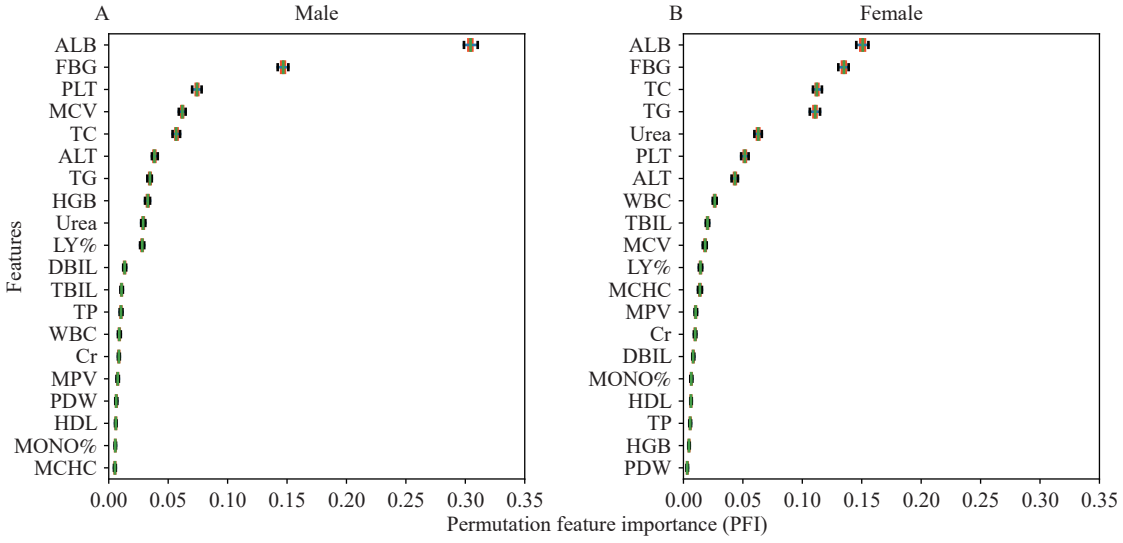
Abbreviation: IFG=Impaired fasting glucose; NFG=Normal fasting glucose.



SUPPLEMENTARY FIGURE S1. Histogram illustrating the distribution of 112,925 individuals across different chronological age groups.



SUPPLEMENTARY FIGURE S2. Heatmap of Pearson correlation between twenty-nine features.
Note: The intensity of color represents the magnitude of the Pearson correlation coefficient.



SUPPLEMENTARY FIGURE S3. Deep Neural Networks age-predictor model's feature importance for (A) male and (B) female subset.