Supplementary Material

List of Abbreviations and Acronyms

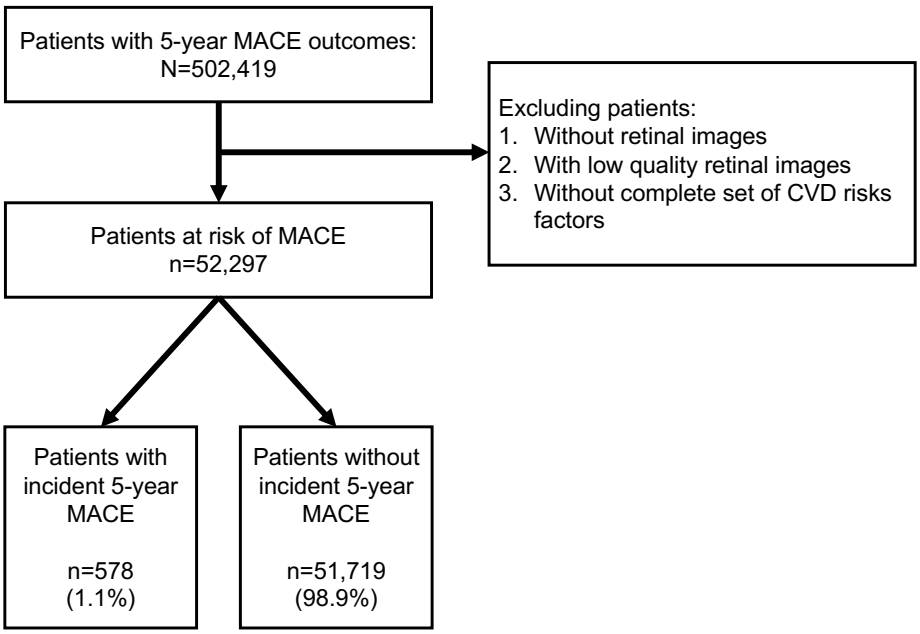
BMI	Body Mass Index
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
SBP	Systolic Blood Pressure
LDL	Low-Density Lipoprotein cholesterol
HDL	High-Density Lipoprotein cholesterol
Trig	Triglycerides
HbA1c	Hemoglobin A1c
MACE	Major Adverse Cardiac Events
SCORE	Systematic COronary Risk Evaluation
AUC	Area Under Curve
PCE	Pooled Cohort Equation
FRA	Framingham risk score
DL	Deep Learning
WHO	World Health Organization
IQR	Interquartile Range
BCE Loss	Binary Cross Entropy Loss
MSE	Mean Squared Error
NRI	Net Reclassification Index
IDI	Integrate Discrimination Index
RGB	Red Green Blue

List of data augmentation in the training

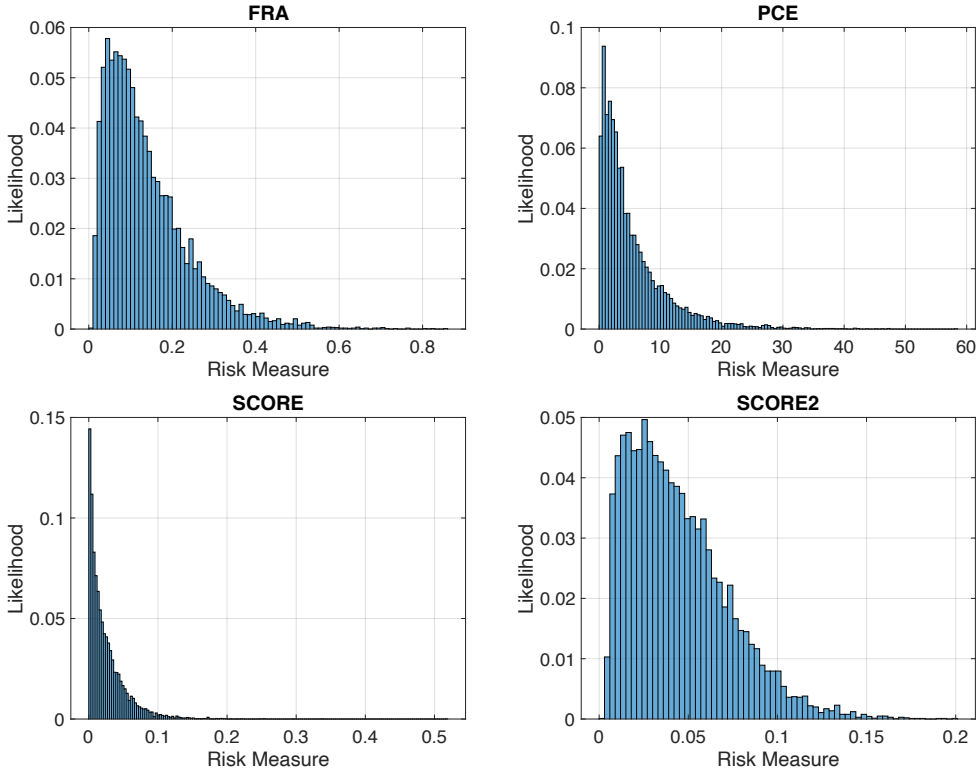
All data augmentation transformation are from Pytorch library.

1. Resize and center crop
2. Color jitter set to (0.2,0.2,0.2)
3. Random Affine transformation set to (180,(0.1,0.1),(0.8,1.2),5,0)
4. Random horizontal flip
5. Random Vertical flip
6. Random Grayscale
7. Gaussian blur set to (5, sigma=(0.1, 2.0))

Supplement Figure 1. Diagram illustrates the flow of data.



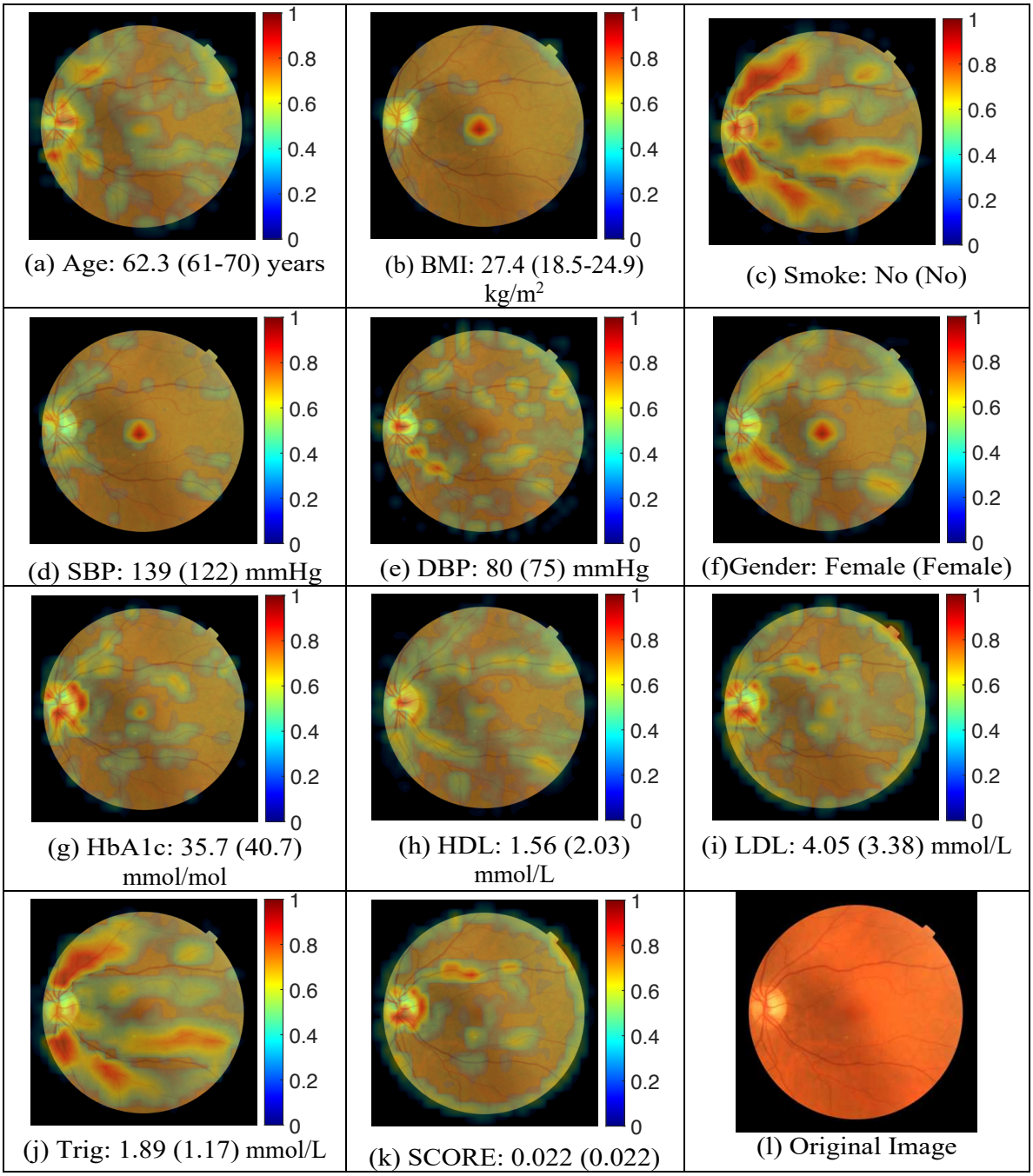
Supplement Figure 2. Distribution of PCE, FRS and SCORE, SCORE2



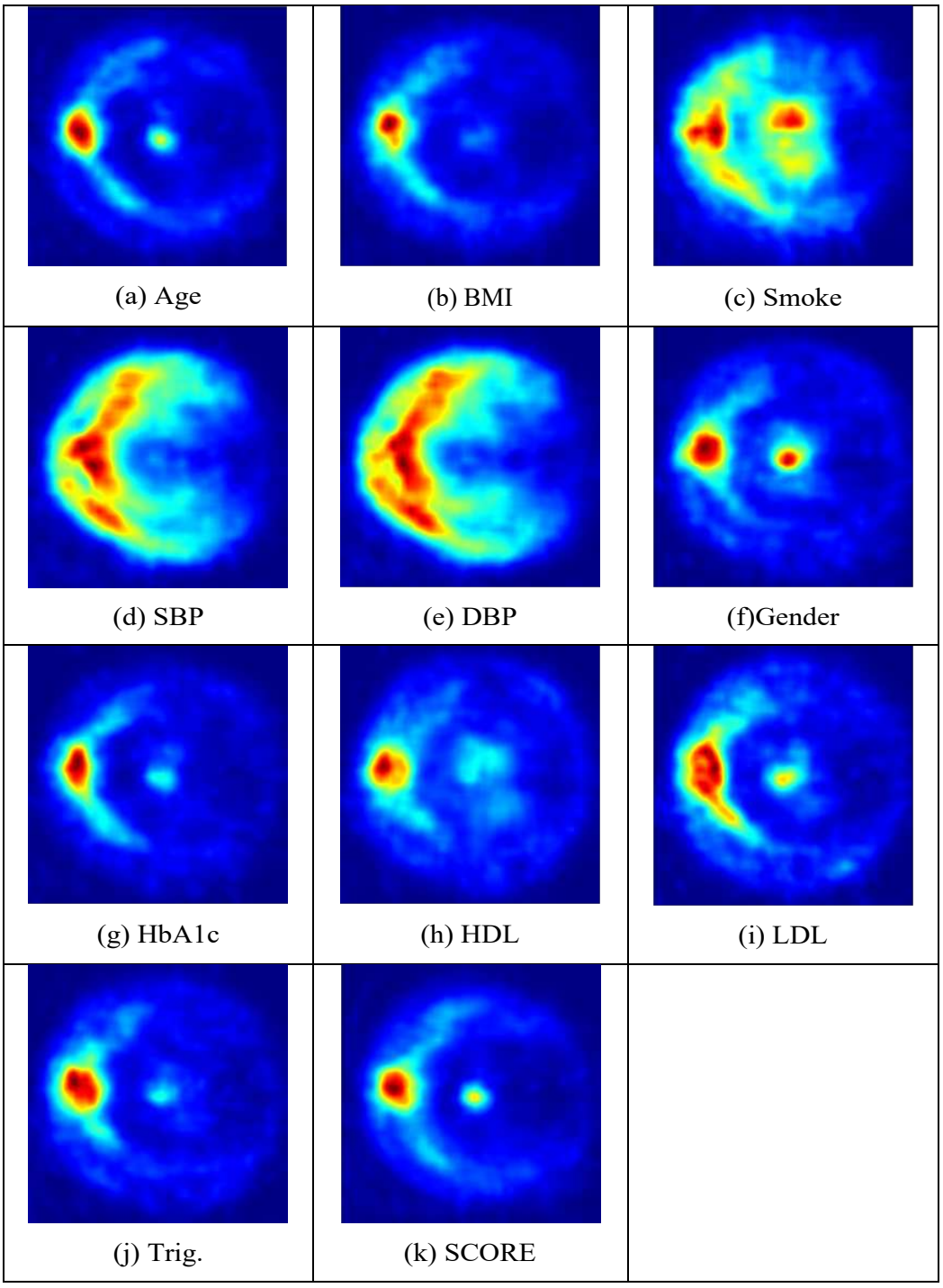
Visualization of the model in the first stage on the retinal image

A modified version of IGOS[18] is implemented in this work (**Figures 3&4**), where the original IGOS algorithm only supports visualization for the classification task, but we are doing regression on CVD risk factors. The IGOS algorithm uses the regressionresults from our XMACE model and traces back to the image pixel that has ahigher impact on the prediction (**Figure 3**). **Figure 4** shows a visualization of attention map aggregate from 3000 samples. From the visualization, we found the disk, fovea and the vessel took the most of attention in the risk prediction. Risk factors such as age, BMI, smoking, gender, HbA1c, HDL cholesterol, LDL cholesterol, and triglycerides have high level of attention at the optic disc and the fovea. Systolic and diastolic blood pressure were linked to the arcade retinal vessels. The statues of the patient's health condition are visualized by a performance polygon diagram (**Figure 5 - 8**). In the figure, the severity of four health indicator: diabetes, hypertension, dyslipidemia, and obesity and the estimated smoke habit are included in the diagram.

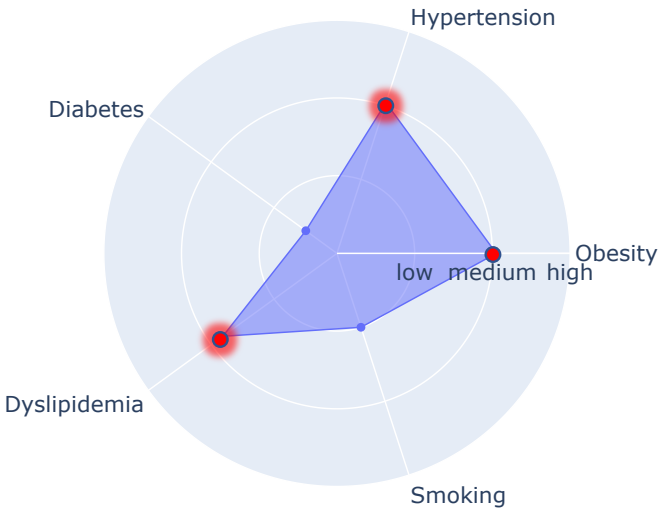
Supplement Figure 3. IGOS Visualization of attention map on features and the estimation value (actual value) of a single patient.



Supplement Figure 4. Aggregated attention map.



Supplement Figure 5. Cardiovascular disease (CVD) risk profiling based on the retinal image: a patient case with high risk of CVD due to obesity and dyslipidemia.

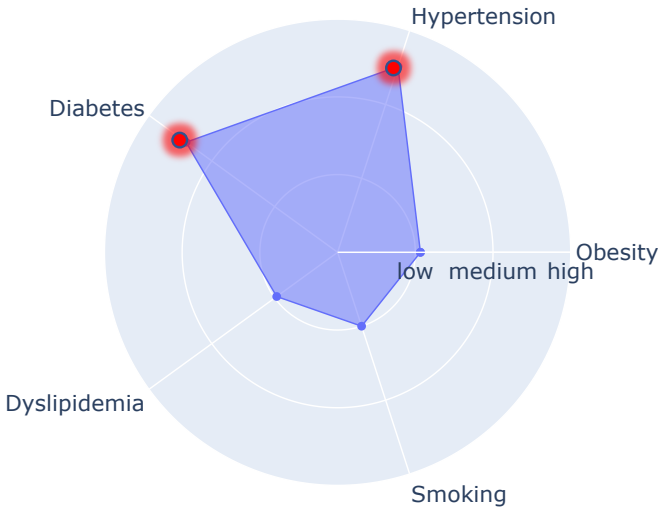


Estimated (actual) results:

Age: 59.3 (41-45) years
SBP: 125.20 (111) mmHg
DBP: 80.08 (75) mmHg
LDL: 3.82 (3.29) mmol/L
Trig.: 1.99 (1.65) mmol/L
HDL: 1.39 (1.10) mmol/L
BMI: 30.88 (25-29.9) kg/m^2
HbA1c: 35.48 (25.6) mmol/mol
Smoke habbit: No (No)
Gender: Female (Female)

5-year MACE risk : No (No)

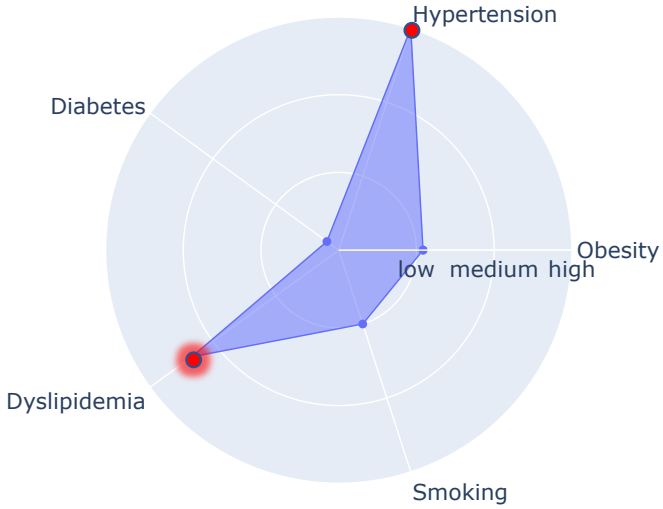
Supplement Figure 6. Cardiovascular disease (CVD) risk profiling based on the retinal image: a patient case with high risk of CVD due to diabetes and hypertension.



Estimated (actual) results:
Age: 57.2 (56-60) years
SBP: 136.35 (159) mmHg
DBP: 79.46 (96) mmHg
LDL: 3.43 (3.95) mmol/L
Trig.: 1.68 (1.43) mmol/L
HDL: 1.54 (1.30) mmol/L
BMI: 26.76 (25-29.9) kg/m^2
HbA1c: 41.83 (36.3) mmol/mol
Smoke habbit: No (No)
Gender: Female (Female)

5-year MACE risk : No (No)

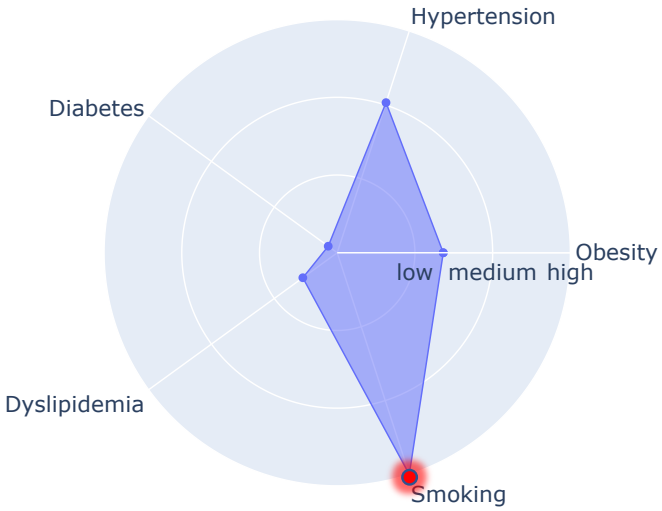
Supplement Figure 7. Cardiovascular disease (CVD) risk profiling based on the retinal image: a case with high risk of CVD due to hypertension and dyslipidemia.



Estimated (actual) results:
Age: 61.73 (61-70) years
SBP: 141.90 (161) mmHg
DBP: 81.64 (90) mmHg
LDL: 3.84 (3.81) mmol/L
Trig.: 1.55 (1.53) mmol/L
HDL: 1.73 (1.51) mmol/L
BMI: 26.70 (25-29.9) kg/m^2
HbA1c: 33.94 (37.0) mmol/mol
Smoke habbit: No (No)
Gender: Female (Female)

5-year MACE risk : No (No)

Supplement Figure 8. Cardiovascular disease (CVD) risk profiling based on the retinal image: a case with high risk of CVD due to hypertension and dyslipidemia.



Estimated (actual) results:
Age: 54.3 (56-60) years
SBP: 129.16 (129) mmHg
DBP: 78.28 (84) mmHg
LDL: 3.33 (3.66) mmol/L
Trig.: 1.50 (2.24) mmol/L
HDL: 1.55 (1.17) mmol/L
BMI: 27.56 (30-34.9) kg/m^2
HbA1c: 37.17 (33.1) mmol/mol
Smoke habbit: Yes (Yes)
Gender: Female (Female)

5-year MACE risk : No (No)

Supplementary Table 1: Classification of risk levels

Health conditions	Obesity	Diabetes	Dyslipidemia	Hypertension	Smoking
Risk indicator	BMI	HbA1c	Total Cholesterol	SBP	Smoking
Low risks	22	38	200	120	False
Medium risks	27	43	220	125	-
High risks	35	48	240	130	True

Supplementary Code 1: Code for PCE calculation

```
def PCE(age,gender,choleterol,HDL,SBP,smoker,diabetes):
    Sex=gender+1
    SystolicBloodPressure=SBP
    Age=age
    Race=0
    TotalCholesterol=choleterol
    HDLCholesterol=HDL
    Smoker=smoker
    Diabetes=diabetes
    LogitFemale = -12.823110 + (0.106501 * Age) + (0.432440 * Race) + (0.000056 *
SystolicBloodPressure**2) + (0.017666 * SystolicBloodPressure) + (0.731678 *
OnHypertensionMed) + (0.943970 * Diabetes) + (1.009790 * Smoker) + (0.151318 *
(TotalCholesterol / HDLCholesterol)) + (-0.008580 * Age * Race) + (-0.003647 *
SystolicBloodPressure * OnHypertensionMed) + (0.006208 * SystolicBloodPressure * Race)
+ (0.152968 * Race * OnHypertensionMed) + (-0.000153 * Age * SystolicBloodPressure) +
(0.115232 * Race * Diabetes) + (-0.092231 * Race * Smoker) + (0.070498 * Race *
(TotalCholesterol / HDLCholesterol)) + (-0.000173 * Race * SystolicBloodPressure *
OnHypertensionMed) + (-0.000094 * Age * SystolicBloodPressure * Race)
    riskFemale = 100 / (1 + np.exp(-LogitFemale))
    LogitMale = -11.679980 + (0.064200 * Age) + (0.482835 * Race) + (-0.000061 *
SystolicBloodPressure**2) + (0.038950 * SystolicBloodPressure) + (2.055533 *
OnHypertensionMed) + (0.842209 * Diabetes) + (0.895589 * Smoker) + (0.193307 *
TotalCholesterol / HDLCholesterol) + (-0.014207 * SystolicBloodPressure *
OnHypertensionMed) + (0.011609 * SystolicBloodPressure * Race) + (-0.119460 *
OnHypertensionMed * Race) + (0.000025 * Age * SystolicBloodPressure) + (-0.077214 *
Race * Diabetes) + (-0.226771 * Race * Smoker) + (-0.117749 * Race * TotalCholesterol
/ HDLCholesterol) + (0.004190 * Race * OnHypertensionMed * SystolicBloodPressure) + (-
0.000199 * Race * Age * SystolicBloodPressure)
    riskMale = 100 / (1 + np.exp(-LogitMale))
    risk = (np.abs(Sex == 1) * riskFemale) + (np.abs(Sex == 2) * riskMale)
    return risk
```

Supplementary Code 2: Code for FRS

```
class FraminghamScoreT():
    def __init__(self):
        self.score='Framingham Score'

    def __woman_CHD(self,age,totalcholeterol,HDL,SBP,smoker,diabetes):
        bx=2.32888*math.log(age)+1.20904*math.log(totalcholeterol) - \
        0.70833*math.log(HDL)+2.76157*math.log(SBP)+0.52873*smoker+0.69154*diabetes
        s=1-0.95012**math.exp(bx-26.1931)
        return s

    def __man_CHD(self,age,totalcholeterol,HDL,SBP,smoker,diabetes):
        bx=3.06117*math.log(age)+1.12370*math.log(totalcholeterol) - \
        0.93263*math.log(HDL)+1.93303*math.log(SBP)+0.65451*smoker+0.57367*diabetes
        s=1-0.88936**math.exp(bx-23.9802)
        return s

    def riskModel(self,age,gender,totalcholeterol,HDL,SBP,smoker,diabetes):
        risk=0
        if gender==1:
            risk=self.__man_CHD(age,totalcholeterol,HDL,SBP,smoker,diabetes)
        else:
            risk=self.__woman_CHD(age,totalcholeterol,HDL,SBP,smoker,diabetes)
        return risk
```

Supplementary Code 3: Code for SCORE:

```
class SCORE():
    def __init__(self):
        self.region='low risk'

    def __wRisk_CHD(self,choleterol, SBP, smoker):
        beta_chol=0.24
        beta_sbp=0.018
        beta_smoker=0.71

        w=beta_chol*(choleterol-6)+beta_sbp*(SBP-120)+beta_smoker*(smoker)
        return w

    def __wRisk_Non_CHD(self,choleterol, SBP, smoker):
        beta_chol=0.02
        beta_sbp=0.022
        beta_smoker=0.63

        w=beta_chol*(choleterol-6)+beta_sbp*(SBP-120)+beta_smoker*(smoker)
        return w
```

```
def __age_Model_note(self, age,alpha,p):
    return math.exp(-(math.exp(alpha))*((age-20)**p))

def __age_Men_CHD(self,age):
    alpha =-22.1
    p=4.71
    return self.__age_Model_note(age,alpha,p)

def __age_Women_CHD(self,age):
    alpha =-29.8
    p=6.36
    return self.__age_Model_note(age,alpha,p)

def __age_Men_Non_CHD(self,age):
    alpha =-26.7
    p=5.64
    return self.__age_Model_note(age,alpha,p)

def __age_Women_Non_CHD(self,age):
    alpha =-31.0
    p=6.62
    return self.__age_Model_note(age,alpha,p)

def __age_w_model_men_CHD(self,age,choleterol,SBP,smoker):
    w=self.__wRisk_CHD(choleterol, SBP, smoker)
    s0=self.__age_Men_CHD(age)
    s=s0**(math.exp(w))
    return s

def __age_w_model_men_Non_CHD(self,age,choleterol,SBP,smoker):
    w=self.__wRisk_Non_CHD(choleterol, SBP, smoker)
    s0=self.__age_Men_Non_CHD(age)
    s=s0**(math.exp(w))
    return s

def __age_w_model_women_CHD(self,age,choleterol,SBP,smoker):
    w=self.__wRisk_CHD(choleterol, SBP, smoker)
    s0=self.__age_Women_CHD(age)
    s=s0**(math.exp(w))
    return s

def __age_w_model_women_Non_CHD(self,age,choleterol,SBP,smoker):
    w=self.__wRisk_Non_CHD(choleterol, SBP, smoker)
    s0=self.__age_Women_Non_CHD(age)
    s=s0**(math.exp(w))
    return s

def riskModel(self,age,gender,choleterol,SBP,smoker,years):
```

```
        if gender==1:
            s=self.__age_w_model_men_CHD(age,choleterol,SBP,smoker)
            sy=self.__age_w_model_men_CHD(age+years,choleterol,SBP,smoker)
            srisk_CHD=1-sy/s
            s=self.__age_w_model_men_Non_CHD(age,choleterol,SBP,smoker)
            sy=self.__age_w_model_men_Non_CHD(age+years,choleterol,SBP,smoker)
            srisk_Non_CHD=1-sy/s
        else:
            s=self.__age_w_model_women_CHD(age,choleterol,SBP,smoker)
            sy=self.__age_w_model_women_CHD(age+years,choleterol,SBP,smoker)
            srisk_CHD=1-sy/s

            s=self.__age_w_model_women_Non_CHD(age,choleterol,SBP,smoker)
            sy=self.__age_w_model_women_Non_CHD(age+years,choleterol,SBP,smoker)
            srisk_Non_CHD=1-sy/s

        return srisk_CHD+srisk_Non_CHD
```

Supplementary Code 4: Code for SCORE2

```
class SCORE2():
    def __init__(self):
        self.region='low risk'

    def riskModel(self,age,gender,choleterol,HDL,SBP,smoker,diabetes):
        self.cage=(age-60)/5
        self.csbp=(SBP-120)/20
        self.ctchol=(choleterol-6)/1
        self.chdl=(HDL-1.3)/0.5
        self.smokewithAge=self.cage*smoker
        self.SBPwithAge=self.cage*self.csbp
        self.TotalCholesterolWithAge=self.cage*self.ctchol
        self.HDLwithAge=self.cage*self.chdl
        self.diabetewithAge=self.cage*diabetes

        if gender==1:

linearPred=0.3742*self.cage+0.6012*smoker+0.2777*self.csbp+0.6457*diabetes+0.1458*self
.ctchol \
                -0.2698*self.chdl-0.0755*self.smokewithAge-0.0255*self.SBPwithAge \
                    -0.0281*self.TotalCholesterolWithAge+0.0426*self.HDLwithAge -
0.0983*self.diabetewithAge

            riskUncalibrated=1-math.pow(0.9605,linearPred)
            riskcalibrated2Low=1-math.exp(-math.exp(-0.5699+0.7476*math.log(-
math.log(1-riskUncalibrated))))
        else:
```

```
linearPred=0.4648*self.cage+0.7744*smoker+0.3131*self.csbp+0.8096*diabetes+0.1002*self
.ctchol \
                -0.2606*self.chdl-0.1088*self.smokewithAge-0.0277*self.SBPwithAge \
                    -0.0226*self.TotalCholesterolWithAge+0.0613*self.HDLwithAge-
0.1272*self.diabetewithAge

            riskUncalibrated=1-math.pow(0.9776,linearPred)
            print(riskUncalibrated)
            riskcalibrated2Low=1-math.exp(-math.exp(-0.7380+0.7019*math.log(-
math.log(1-riskUncalibrated))))

        return riskcalibrated2Low
```