

# Risk Prediction in the Framingham Heart Study

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Framingham Heart Study

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# Framingham Heart Study

The Framingham Heart Study is a project of Boston University & the National Heart, Lung, & Blood Institute.

ABOUT PARTICIPANTS INVESTIGATORS RISK FUNCTIONS BIBLIOGRAPHY FOR RESEARCHERS

**FHS Risk Functions**

**Atrial Fibrillation**

FHS AF score (10-year risk)  
Heart Failure in Atrial Fibrillation (10-year risk)

**Cardiovascular Disease**

Cardiovascular Disease (10-year risk)  
Cardiovascular Disease (30-year risk)

**Congestive Heart Failure**

**Coronary Heart Disease**

Hard Coronary Heart Disease (10-year risk)  
Coronary Heart Disease (10-year risk)  
Enfermedad coronaria (riesgo a 10 años)  
Recurrent Coronary Heart Disease  
Coronary Heart Disease (2-year risk) – Second Event

**Diabetes**

**Fatty Liver Disease**

**Hypertension**

**Intermittent**

**Stroke**

Stroke  
Stroke after Atrial Fibrillation  
Stroke or Death after Atrial Fibrillation

# FHS: A Long History of Risk Prediction

- Kannel, McGee, Gordon 1976 - separate calculations for men & women
  - Sex, Age, SBP, TC, Glucose Intolerance, ECG-LVH, Smoking in logistic model
  - CHD risk over 8 years of follow up
  - 10% at highest risk were 20% of CHD events over 8 years
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- Wilson PWF et al 1998 – Cox PH, LDL-C, categories, points, CHD 10-yr risk
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# FHS: A Long History of Risk Prediction (Women)

Wilson et al 1998

Step 1

| Age   |         |          |
|-------|---------|----------|
| Years | LDL Pts | Chol Pts |
| 30-34 | -9      | [-9]     |
| 35-39 | -4      | [-4]     |
| 40-44 | 0       | [0]      |
| 45-49 | 3       | [3]      |
| 50-54 | 6       | [6]      |
| 55-59 | 7       | [7]      |
| 60-64 | 8       | [8]      |
| 65-69 | 8       | [8]      |
| 70-74 | 8       | [8]      |

Step 2

| LDL - C |           |         |
|---------|-----------|---------|
| (mg/dl) | (mmol/L)  | LDL Pts |
| <100    | <2.59     | -2      |
| 100-129 | 2.60-3.36 | 0       |
| 130-159 | 3.37-4.14 | 0       |
| 160-190 | 4.15-4.92 | 2       |
| ≥190    | ≥4.92     | 2       |

| Cholesterol |           |          |
|-------------|-----------|----------|
| (mg/dl)     | (mmol/L)  | Chol Pts |
| <160        | <4.14     | [-2]     |
| 160-199     | 4.15-5.17 | [0]      |
| 200-239     | 5.18-6.21 | [1]      |
| 240-279     | 6.22-7.24 | [1]      |
| ≥280        | ≥7.25     | [3]      |

Step 3

| HDL - C |           |         |          |
|---------|-----------|---------|----------|
| (mg/dl) | (mmol/L)  | LDL Pts | Chol Pts |
| <35     | <0.90     | 5       | [5]      |
| 35-44   | 0.91-1.16 | 2       | [2]      |
| 45-49   | 1.17-1.29 | 1       | [1]      |
| 50-59   | 1.30-1.55 | 0       | [0]      |
| ≥60     | ≥1.56     | -2      | [-3]     |

Step 4

| Blood Pressure   |                   |           |           |           |
|------------------|-------------------|-----------|-----------|-----------|
| Systolic (mm Hg) | Diastolic (mm Hg) |           |           |           |
|                  | <80               | 80-84     | 85-89     | 90-99     |
| <120             | -3 [-3] pts       |           |           |           |
| 120-129          |                   | 0 [0] pts |           |           |
| 130-139          |                   |           | 0 [0] pts |           |
| 140-159          |                   |           |           | 2 [2] pts |
| ≥160             |                   |           |           | 3 [3] pts |

+ Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

| Diabetes |         |          |
|----------|---------|----------|
|          | LDL Pts | Chol Pts |
| No       | 0       | [0]      |
| Yes      | 4       | [4]      |

Step 6

| Smoker |         |          |
|--------|---------|----------|
|        | LDL Pts | Chol Pts |
| No     | 0       | [0]      |
| Yes    | 2       | [2]      |

(sum from steps 1-6)

Step 7

| Adding up the points |       |
|----------------------|-------|
| Age                  | _____ |
| LDL-C or Chol        | _____ |
| HDL - C              | _____ |
| Blood Pressure       | _____ |
| Diabetes             | _____ |
| Smoker               | _____ |
| Point total          | _____ |

(determine CHD risk from point total)

Step 8

| CHD Risk |                |          |                |
|----------|----------------|----------|----------------|
| LDL Pts  | 10 Yr CHD Risk | Chol Pts | 10 Yr CHD Risk |
| ≤-2      | 1%             | ≤-2      | [1%]           |
| -1       | 2%             | [-1]     | [2%]           |
| 0        | 2%             | [0]      | [2%]           |
| 1        | 2%             | [1]      | [2%]           |
| 2        | 3%             | [2]      | [3%]           |
| 3        | 3%             | [3]      | [3%]           |
| 4        | 4%             | [4]      | [4%]           |
| 5        | 5%             | [5]      | [4%]           |
| 6        | 6%             | [6]      | [5%]           |
| 7        | 7%             | [7]      | [6%]           |
| 8        | 8%             | [8]      | [7%]           |
| 9        | 9%             | [9]      | [8%]           |
| 10       | 11%            | [10]     | [10%]          |
| 11       | 13%            | [11]     | [11%]          |
| 12       | 15%            | [12]     | [13%]          |
| 13       | 17%            | [13]     | [15%]          |
| 14       | 20%            | [14]     | [18%]          |
| 15       | 24%            | [15]     | [20%]          |
| 16       | 27%            | [16]     | [24%]          |
| ≥17      | ≥32%           | ≥17      | ≥27%           |

(compare to average person your age)

Step 9

| Comparative Risk |                        |                              |                      |
|------------------|------------------------|------------------------------|----------------------|
| Age (years)      | Average 10 Yr CHD Risk | Average 10 Yr Hard* CHD Risk | Low** 10 Yr CHD Risk |
| 30-34            | <1%                    | <1%                          | <1%                  |
| 35-39            | <1%                    | <1%                          | 1%                   |
| 40-44            | 2%                     | 1%                           | 2%                   |
| 45-49            | 5%                     | 2%                           | 3%                   |
| 50-54            | 8%                     | 3%                           | 5%                   |
| 55-59            | 12%                    | 7%                           | 7%                   |
| 60-64            | 12%                    | 8%                           | 8%                   |
| 65-69            | 13%                    | 8%                           | 8%                   |
| 70-74            | 14%                    | 11%                          | 8%                   |

\* Hard CHD events exclude angina pectoris

\*\* Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dL, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Key

| Color  | Relative Risk |
|--------|---------------|
| green  | Very low      |
| white  | Low           |
| yellow | Moderate      |
| rose   | High          |
| red    | Very high     |

# FHS: A Long History of Risk Prediction (Women)

(determine CHD risk from point total)

Step 8

| CHD Risk         |                   |                   |                   |
|------------------|-------------------|-------------------|-------------------|
| LDL Pts<br>Total | 10 Yr<br>CHD Risk | Chol Pts<br>Total | 10 Yr<br>CHD Risk |
| ≤-2              | 1%                | [≤-2]             | [1%]              |
| -1               | 2%                | [-1]              | [2%]              |
| 0                | 2%                | [0]               | [2%]              |
| 1                | 2%                | [1]               | [2%]              |
| 2                | 3%                | [2]               | [3%]              |
| 3                | 3%                | [3]               | [3%]              |
| 4                | 4%                | [4]               | [4%]              |
| 5                | 5%                | [5]               | [4%]              |
| 6                | 6%                | [6]               | [5%]              |
| 7                | 7%                | [7]               | [6%]              |
| 8                | 8%                | [8]               | [7%]              |
| 9                | 9%                | [9]               | [8%]              |
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| ≥17              | ≥32%              | [≥17]             | [≥27%]            |

(compare to average person your age)

Step 9

| Comparative Risk |                              |                                    |                            |
|------------------|------------------------------|------------------------------------|----------------------------|
| Age<br>(years)   | Average<br>10 Yr CHD<br>Risk | Average<br>10 Yr Hard* CHD<br>Risk | Low**<br>10 Yr CHD<br>Risk |
| 30-34            | <1%                          | <1%                                | <1%                        |
| 35-39            | <1%                          | <1%                                | 1%                         |
| 40-44            | 2%                           | 1%                                 | 2%                         |
| 45-49            | 5%                           | 2%                                 | 3%                         |
| 50-54            | 8%                           | 3%                                 | 5%                         |
| 55-59            | 12%                          | 7%                                 | 7%                         |
| 60-64            | 12%                          | 8%                                 | 8%                         |
| 65-69            | 13%                          | 8%                                 | 8%                         |
| 70-74            | 14%                          | 11%                                | 8%                         |

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FHS AF score (10-year risk)  
Heart Failure in Atrial Fibrillation (10-year risk)

### Cardiovascular Disease

Cardiovascular Disease (10-year risk)  
Cardiovascular Disease (30-year risk)

### Congestive Heart Failure

## Coronary Heart Disease

Hard Coronary Heart Disease (10-year risk)  
Coronary Heart Disease (10-year risk)  
Enfermedad coronaria (riesgo a 10 años)  
Recurrent Coronary Heart Disease  
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## Diabetes

### Fatty Liver Disease

### Hypertension

### Intermittent

## Stroke

Stroke  
Stroke after Atrial Fibrillation  
Stroke or Death after Atrial Fibrillation

# FHS: A Long History of Risk Prediction: Computerized

- **Cardiovascular Disease (10-year risk)**

- **Predictors**

- Age
- Diabetes
- Smoking
- Treated and untreated Systolic Blood Pressure
- Total cholesterol
- HDL cholesterol
- BMI replacing lipids in a simpler model

- **Risk Score Calculators**

- **Interactive**

- **Excel spreadsheets**



# FHS: A Long History of Risk Prediction: Computerized

## General CVD Risk Prediction Using Lipids

Sex:

☐ M ☒ F

Age (years):

40

Systolic Blood Pressure (mmHg):

125

Treatment for Hypertension:

☐ Yes ☒ No

Current smoker:

☐ Yes ☒ No

Diabetes:

☐ Yes ☒ No

HDL:

45

Total Cholesterol:

180

Calculate

Your Heart/Vascular Age: 0

| 10 Year Risk           |           |    |
|------------------------|-----------|----|
| <div><div></div></div> | Your risk | 0% |
| <div><div></div></div> | Normal    | 0% |
| <div><div></div></div> | Optimal   | 0% |

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Sex:

☐ M ☒ F

Age (years):

40

Systolic Blood Pressure (mmHg):

125

Treatment for Hypertension:

☐ Yes ☒ No

Current smoker:

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Diabetes:

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HDL:

45

Total Cholesterol:

180

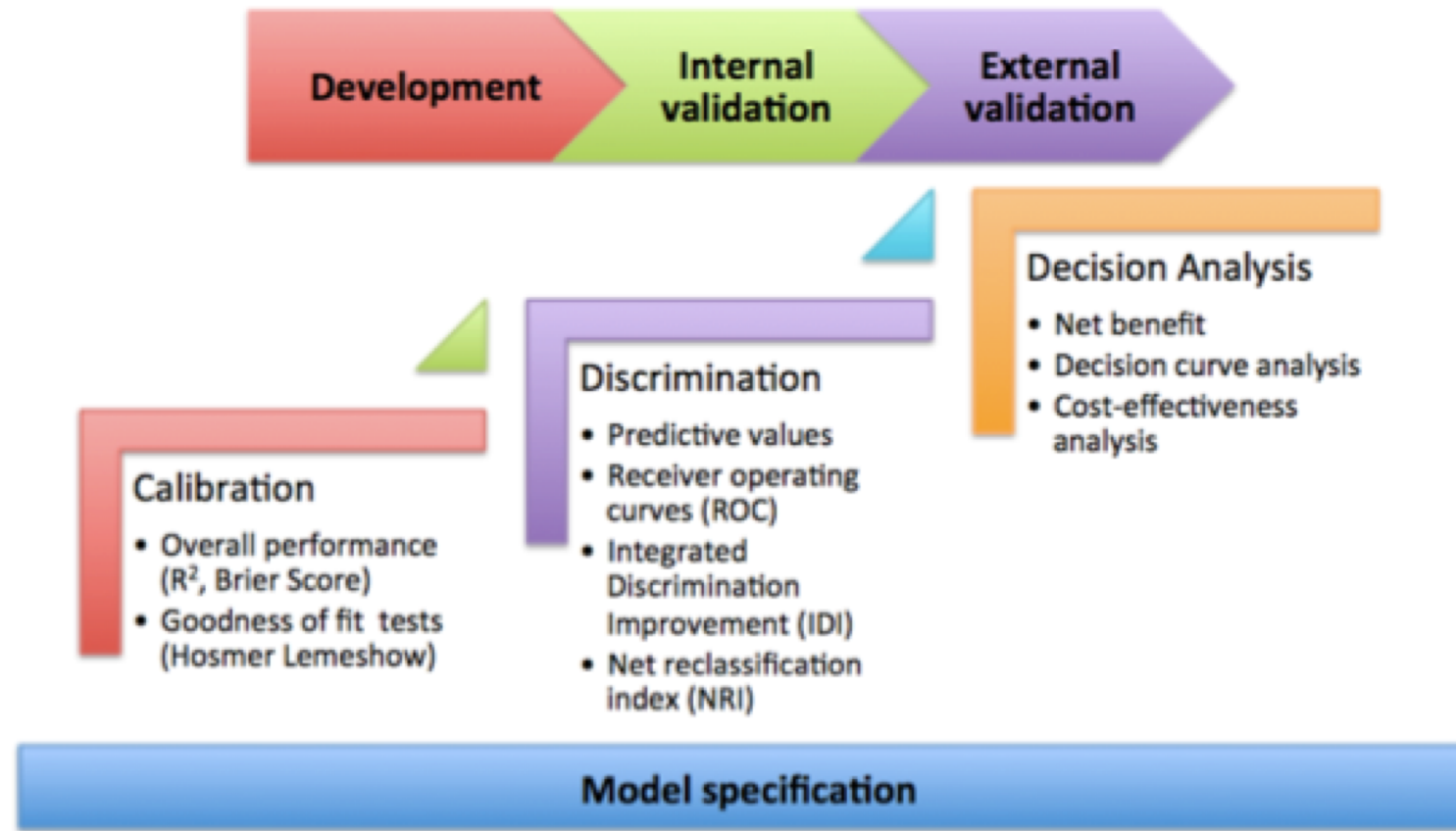
Calculate

Your Heart/Vascular Age: 40

| 10 Year Risk           |           |      |
|------------------------|-----------|------|
| <div><div></div></div> | Your risk | 2.5% |
| <div><div></div></div> | Normal    | 2.5% |
| <div><div></div></div> | Optimal   | 1.3% |

# Evaluating the performance of risk prediction models

## Three Steps of Evaluation



<https://www.mailman.columbia.edu/research/population-health-methods/risk-prediction>

# Evaluating the performance of risk prediction models

## Three Steps of Evaluation

- Step 1. Calibration: how well do model-based estimates align with observed outcomes?
  - Hosmer-Lemeshow Test: Do the number of observed cases across quantiles (deciles) match well with the expected based on the model? – Chi-square test
- Step 2. Discrimination: how well a model differentiates between subjects who will have the outcome from those who will not?
  - AUC: area under the ROC curve, C Statistic
  - Net Reclassification Index: upon adding a variable to the model, is a diseased person classified at higher risk and a non-diseased person at lower risk
- Step 3. Decision analysis: how and when will the predictions impact actual decisions?

<https://www.mailman.columbia.edu/research/population-health-methods/risk-prediction>

# Pooled Cohort Equations Risk Calculations

- 2013 Guidelines by joint effort of ACC and AHA
  - Lloyd-Jones et al Circ 2014
- ASCVD: atherosclerotic CVD – hard CHD, CHD death, hard stroke, stroke death
- Based on results from
  - ARIC (Atherosclerosis Risk in Communities) Study
  - Cardiovascular Health Study
  - CARDIA (Coronary Artery Risk Development in Young Adults) study
  - Framingham original and offspring cohorts
- Developed a model analyzing pooled data from each study using Cox Proportional Regression Analysis to obtain 10-year Risk Predictions

# Pooled Cohort Equations (PCE) Risk Calculations

Lloyd-Jones et al  
2013 ACC/AHA Guidelines

**Table A. Equation Parameters of the Pooled Cohort Equations for Estimation of 10-Year Risk of Hard ASCVD\* and Specific Examples for Each Race and Sex Group**

|                                                                                                                                                     | White       |                          |                      | African American |                          |                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------|--------------------------|----------------------|------------------|--------------------------|----------------------|
|                                                                                                                                                     | Coefficient | Individual Example Value | Coefficient × Value† | Coefficient      | Individual Example Value | Coefficient × Value† |
| Women (Example: 55 years of age with total cholesterol 213 mg/dL, HDL-C 50 mg/dL, untreated systolic BP 120 mm Hg, nonsmoker, and without diabetes) |             |                          |                      |                  |                          |                      |
| Ln Age (y)                                                                                                                                          | -29.799     | 4.01                     | -119.41              | 17.114           | 4.01                     | 68.58                |
| Ln Age, Squared                                                                                                                                     | 4.884       | 16.06                    | 78.44                | N/A              | N/A                      | N/A                  |
| Ln Total Cholesterol (mg/dL)                                                                                                                        | 13.540      | 5.36                     | 72.59                | 0.940            | 5.36                     | 5.04                 |
| Ln Age × Ln Total Cholesterol                                                                                                                       | -3.114      | 21.48                    | -66.91               | N/A              | N/A                      | N/A                  |
| Ln HDL-C (mg/dL)                                                                                                                                    | -13.578     | 3.91                     | -53.12               | -18.920          | 3.91                     | -74.01               |
| Ln Age × Ln HDL-C                                                                                                                                   | 3.149       | 15.68                    | 49.37                | 4.475            | 15.68                    | 70.15                |
| Ln Treated Systolic BP (mm Hg)                                                                                                                      | 2.019       | —                        | —                    | 29.291           | —                        | —                    |
| Ln Age × Ln Treated Systolic BP                                                                                                                     | N/A         | N/A                      | N/A                  | -6.432           | —                        | —                    |
| Ln Untreated Systolic BP (mm Hg)                                                                                                                    | 1.957       | 4.79                     | 9.37                 | 27.820           | 4.79                     | 133.19               |
| Ln Age × Ln Untreated Systolic BP                                                                                                                   | N/A         | N/A                      | N/A                  | -6.087           | 19.19                    | -116.79              |
| Current Smoker (1=Yes, 0=No)                                                                                                                        | 7.574       | 0                        | 0                    | 0.691            | 0                        | 0                    |
| Ln Age × Current Smoker                                                                                                                             | -1.665      | 0                        | 0                    | N/A              | N/A                      | N/A                  |
| Diabetes (1=Yes, 0=No)                                                                                                                              | 0.661       | 0                        | 0                    | 0.874            | 0                        | 0                    |
| Individual Sum                                                                                                                                      |             |                          | -29.67               |                  |                          | 86.16                |
| Mean (Coefficient × Value)                                                                                                                          | N/A         | N/A                      | -29.18               | N/A              | N/A                      | 86.61                |
| Baseline Survival                                                                                                                                   | N/A         | N/A                      | 0.9665               | N/A              | N/A                      | 0.9533               |
| Estimated 10-y Risk of Hard ASCVD                                                                                                                   | N/A         | N/A                      | 2.1%                 | N/A              | N/A                      | 3.0%                 |
| Men (Example: 55 years of age with total cholesterol 213 mg/dL, HDL-C 50 mg/dL, untreated systolic BP 120 mm Hg, nonsmoker, and without diabetes)   |             |                          |                      |                  |                          |                      |
| Ln Age (y)                                                                                                                                          | 12.344      | 4.01                     | 49.47                | 2.469            | 4.01                     | 9.89                 |
| Ln Total Cholesterol (mg/dL)                                                                                                                        | 11.853      | 5.36                     | 63.55                | 0.302            | 5.36                     | 1.62                 |
| Ln Age × Ln Total Cholesterol                                                                                                                       | -2.664      | 21.48                    | -57.24               | N/A              | N/A                      | N/A                  |
| Ln HDL-C (mg/dL)                                                                                                                                    | -7.990      | 3.91                     | -31.26               | -0.307           | 3.91                     | -1.20                |
| Ln Age × Ln HDL-C                                                                                                                                   | 1.769       | 15.68                    | 27.73                | N/A              | N/A                      | N/A                  |
| Ln Treated Systolic BP (mm Hg)                                                                                                                      | 1.797       | —                        | —                    | 1.916            | —                        | —                    |
| Ln Untreated Systolic BP (mm Hg)                                                                                                                    | 1.764       | 4.79                     | 8.45                 | 1.809            | 4.79                     | 8.66                 |
| Current Smoker (1=Yes, 0=No)                                                                                                                        | 7.837       | 0                        | 0                    | 0.549            | 0                        | 0                    |
| Ln Age × Current Smoker                                                                                                                             | -1.795      | 0                        | 0                    | N/A              | N/A                      | N/A                  |
| Diabetes (1=Yes, 0=No)                                                                                                                              | 0.658       | 0                        | 0                    | 0.645            | 0                        | 0                    |
| Individual Sum                                                                                                                                      |             |                          | 60.69                |                  |                          | 18.97                |
| Mean (Coefficient × Value)                                                                                                                          | N/A         | N/A                      | 61.18                | N/A              | N/A                      | 19.54                |
| Baseline Survival                                                                                                                                   | N/A         | N/A                      | 0.9144               | N/A              | N/A                      | 0.8954               |
| Estimated 10-y Risk of Hard ASCVD                                                                                                                   | N/A         | N/A                      | 5.3%                 | N/A              | N/A                      | 6.1%                 |

\*Defined as first occurrence of nonfatal myocardial infarction or CHD death, or fatal or nonfatal stroke.

†Coefficient × Value: For age, lipids, and BP, defined as the natural log of the value multiplied by the parameter estimate. When an age interaction is present with lipids or BP, the natural log of age is multiplied by the natural log of the lipid or BP, and the result is multiplied by the parameter estimate. N/A indicates that that specific covariate was not included in the model for that sex-race group; — indicates that this value was not included in the example (eg, this example used untreated systolic BP, not treated systolic BP).

ASCVD indicates atherosclerotic cardiovascular disease; BP indicates blood pressure; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; Ln, natural logarithm; and N/A, not included.

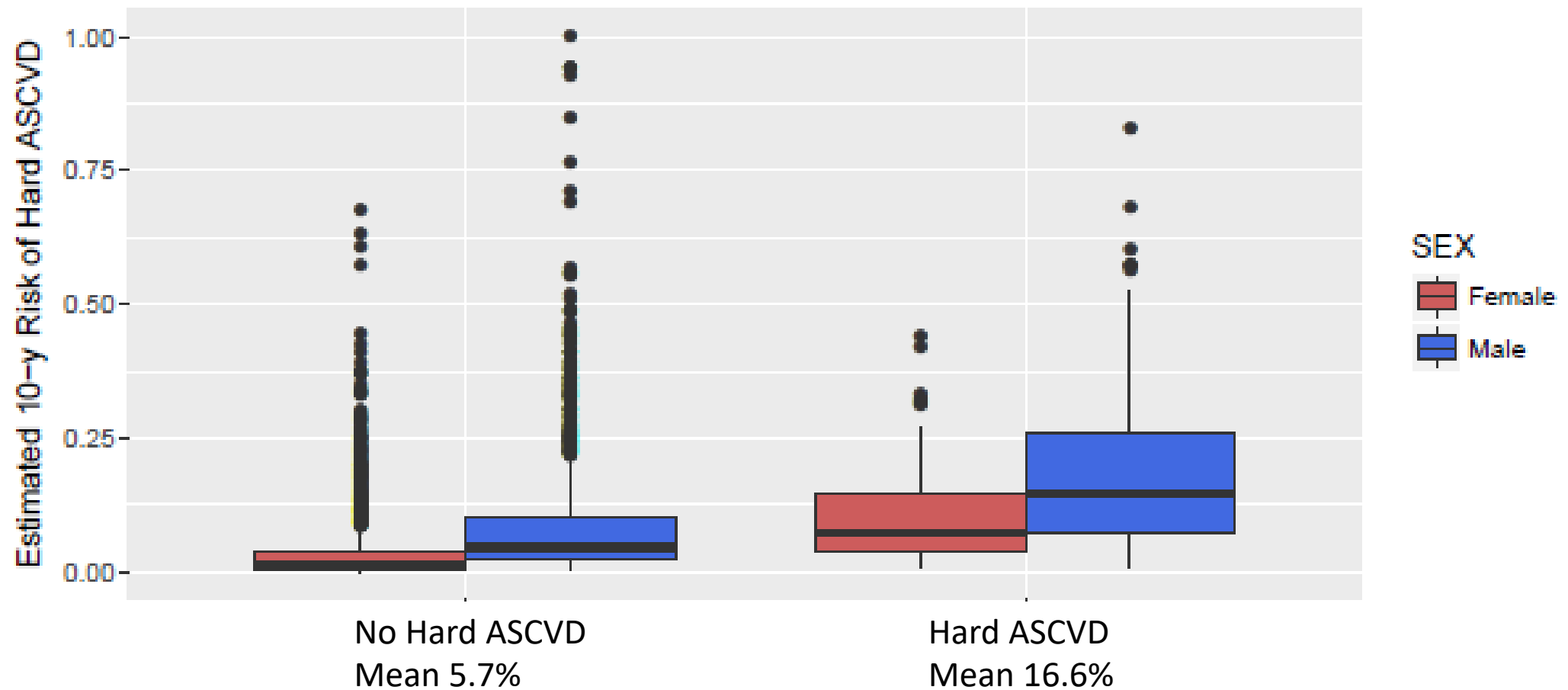
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# PCE Risk Calculations in Framingham (FHS)

- Sample: (Limitation – FHS data used for prediction)
  - 4921 Framingham Heart Study Participants, 198 events over follow-up
    - 2904 Offspring aged 40-80 at Exam 5 (1991-1995)
    - 2017 Gen3 aged 40-80 at Exam 1 (2002-2005)
  - Hard Atherosclerotic disease, as defined by ACC/AHA 2013 Guidelines
    - hard CHD (recognized MI, CHD death), hard Stroke (stroke, stroke death)
  - Follow-up Time: up to 10 years
- PCE deviations: Calculated sex-specific PCE sums and subtracted PCE sex-specific mean sum of covariates
- Obtained risk estimates
- Used PCE deviations from the mean in Cox PH model

# People with events have higher risk

## Men have higher risk than Women

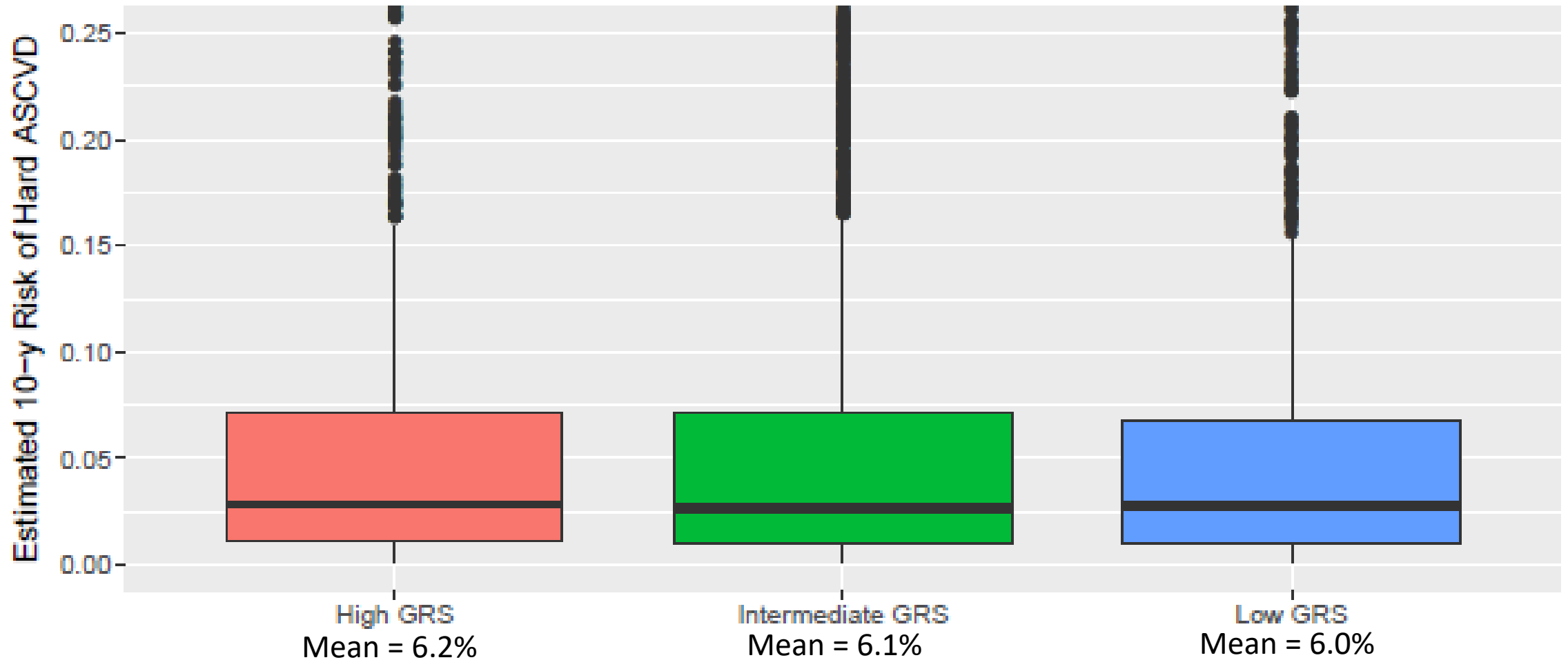


# Genetic Risk Score (GRS) for CHD

- 1000G analysis by CARDIoGRAMplusC4D Consortium, Nikpay et al Nat Genet 2015
  - Case-Control Study (77% European ancestry) – N=184,305
    - 60,801 Coronary Artery Disease Cases
    - 123,504 Controls
  - Evaluated ~9M variants
- For GRS we used 57 variants significant in either additive or recessive models at  $p < 5 \times 10^{-8}$  (Table 1 and Supplementary Table 2)
- Calculated weighted sum of variants, with regression coefficients from additive models in Nikpay paper as weights



# GRS score independent of Risk from Traditional Risk Factors



# Cox Regression Model Statistics

## FHS Men and Women Combined

### Analysis of Maximum Likelihood Estimates

| Parameter     | Effect Estimate | Standard Error | Chi-Square | Pr > ChiSq | Hazard Ratio |
|---------------|-----------------|----------------|------------|------------|--------------|
| PCE deviation | 0.890           | 0.065          | 187.22     | <.0001     | 2.44         |

### Analysis of Maximum Likelihood Estimates

| Parameter     | Effect Estimate | Standard Error | Chi-Square | Pr > ChiSq | Hazard Ratio |
|---------------|-----------------|----------------|------------|------------|--------------|
| PCE deviation | 0.892           | 0.065          | 188.12     | <.0001     | 2.44         |
| GRS           | 0.773           | 0.195          | 15.77      | <.0001     | 2.17         |

# Calibration and Discrimination Statistics

## FHS Men and Women Combined

| Predictors          | Calibration Statistics* |                  | Discrimination Statistics |                            |                |
|---------------------|-------------------------|------------------|---------------------------|----------------------------|----------------|
|                     | Calib<br>chisq          | Calib<br>P value | C Statistic<br>(95% CI)   | Continuous NRI<br>(95% CI) | NRI<br>P value |
| PCE deviation       | 7.91                    | 0.544            | 0.783<br>(0.756, 0.810)   |                            |                |
| PCE deviation + GRS | 6.24                    | 0.716            | 0.793<br>(0.767, 0.82)    | 0.097<br>(0.022, 0.177)    | 0.013          |

\*Adjusted Hosmer-Lemeshow Calibration Statistics

- Both PCE and PCE+GRS have good calibration (not significant)
- Adding GRS to PCE provides improved discrimination
- Caveat PCE equations used FHS data

# Summary

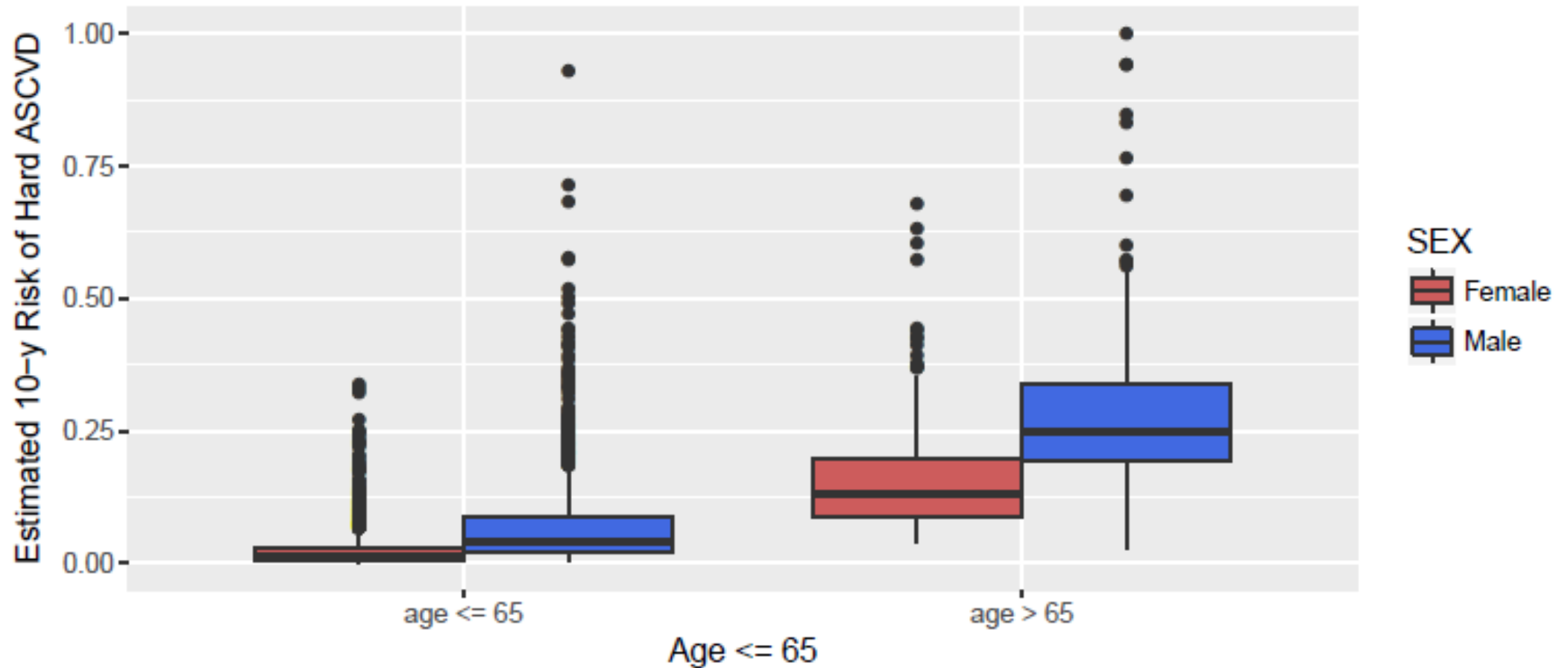
- Long History of Risk Prediction
- Risk Prediction is Commonly Used in the Clinic Today
  - Subjects with Risk  $> 7.5\%$  are recommended for treatment
- PCE Equations are recommended by ACC/AHA for use in the Clinic
- In FHS, PCE equations produce risk estimates that have good fit and discriminate those with events from those without
  - Caveat: FHS used in development of PCE Equations
  - Risk is about 2.4 times higher per unit increase of PCE sum
- In FHS, GRS score for CHD adds significantly to risk for hard ASCVD, increasing risk about 2.2 times per unit increase in GRS

# Acknowledgements

- Framingham Heart Study Participants
- NHLBI for > 70 years of support
- Many researchers in FHS
  - Especially those who pursued Risk Prediction
    - William Kannel
    - Peter Wilson
    - Ralph D'Agostino
    - Michael Pencina



# Those with Age $\leq 65$ have lower risk



# Calibration, Discrimination for Men, Women

| Sample | N    | Predictors             | Calibration Statistics |                | Discrimination Statistics |                            |         |
|--------|------|------------------------|------------------------|----------------|---------------------------|----------------------------|---------|
|        |      |                        | Adj Calib<br>chisq     | Adj<br>P value | C Statistic<br>(95% CI)   | Continuous NRI<br>(95% CI) | NRI.p   |
| Women  | 2662 | PCE_dev                | 4.781                  | 0.853          | 0.824<br>(0.783, 0.865)   |                            |         |
| Women  | 2662 | PCE_dev + GRS          | 5.008                  | 0.834          | 0.829<br>(0.789, 0.869)   | 0.135<br>(-0.042, 0.261)   | 0.106   |
| Women  | 2662 | PCE_dev+highGRS+intGRS | 6.523                  | 0.687          | 0.828<br>(0.789, 0.867)   | 0.072<br>(-0.132, 0.200)   | 0.12    |
| Men    | 2259 | PCE_dev                | 8.322                  | 0.502          | 0.760<br>(0.723, 0.797)   |                            |         |
| Men    | 2259 | PCE_dev+GRS            | 4.299                  | 0.891          | 0.776<br>(0.739, 0.813)   | 0.119<br>(0.043, 0.215)    | 0.00664 |
| Men    | 2259 | PCE_dev+highGRS+intGRS | 3.767                  | 0.926          | 0.768<br>(0.732, 0.805)   | 0.084<br>(0.030, 0.278)    | 0.033   |



# Calibration and Discrimination Statistics Men and Women Combined

| Predictors             | Calibration Statistics* |                  | Discrimination Statistics |                            |       |
|------------------------|-------------------------|------------------|---------------------------|----------------------------|-------|
|                        | Calib<br>chisq          | Calib<br>P value | C Statistic<br>(95% CI)   | Continuous NRI<br>(95% CI) | NRI.p |
| PCE_dev                | 7.91                    | 0.544            | 0.783<br>(0.756, 0.810)   |                            |       |
| PCE_dev+GRS            | 6.24                    | 0.716            | 0.793<br>(0.767, 0.82)    | 0.097<br>(0.022, 0.177)    | 0.013 |
| PCE_dev+highGRS+intGRS | 6.45                    | 0.694            | 0.788<br>(0.761, 0.815)   | 0.0657<br>(-0.09, 0.153)   | 0.093 |

\*Adjusted Calibration Statistics

# FHS: A Long History of Risk Prediction: Wikipedia

- **Framingham Risk Score for Women**
- **Age:** 20–34 years: Minus 7 points. 35–39 years: Minus 3 points. 40–44 years: 0 points. 45–49 years: 3 points. 50–54 years: 6 points. 55–59 years: 8 points. 60–64 years: 10 points. 65–69 years: 12 points. 70–74 years: 14 points. 75–79 years: 16 points.
- **Total cholesterol, mg/dL:** Age 20–39 years: Under 160: 0 points. 160-199: 4 points. 200-239: 8 points. 240-279: 11 points. 280 or higher: 13 points. • Age 40–49 years: Under 160: 0 points. 160-199: 3 points. 200-239: 6 points. 240-279: 8 points. 280 or higher: 10 points. • Age 50–59 years: Under 160: 0 points. 160-199: 2 points. 200-239: 4 points. 240-279: 5 points. 280 or higher: 7 points. • Age 60–69 years: Under 160: 0 points. 160-199: 1 point. 200-239: 2 points. 240-279: 3 points. 280 or higher: 4 points. • Age 70–79 years: Under 160: 0 points. 160-199: 1 point. 200-239: 1 point. 240-279: 2 points. 280 or higher: 2 points.
- **If cigarette smoker:** Age 20–39 years: 9 points. • Age 40–49 years: 7 points. • Age 50–59 years: 4 points. • Age 60–69 years: 2 points. • Age 70–79 years: 1 point.
- **All non smokers:** 0 points.
- **HDL cholesterol, mg/dL:** 60 or higher: Minus 1 point. 50-59: 0 points. 40-49: 1 point. Under 40: 2 points.
- **Systolic blood pressure, mm Hg:** Untreated: Under 120: 0 points. 120-129: 1 point. 130-139: 2 points. 140-159: 3 points. 160 or higher: 4 points. • Treated: Under 120: 0 points. 120-129: 3 points. 130-139: 4 points. 140-159: 5 points. 160 or higher: 6 points.
- **10-year risk in %:** Points total: Under 9 points: <1%. 9-12 points: 1%. 13-14 points: 2%. 15 points: 3%. 16 points: 4%. 17 points: 5%. 18 points: 6%. 19 points: 8%. 20 points: 11%. 21=14%, 22=17%, 23=22%, 24=27%, >25= Over 30%

# Polygenic Risk Score

- Polygenic Risk Score: using multiple genetic variants to obtain an estimate of genetic burden of risk for disease
  - Usually calculated as weighted sum of genotypes a person carries weighted by regression coefficient measuring impact of genetic variant on disease
- Early efforts: used sum a few genetic variants identified in GWAS
- Example (Meigs et al 2008)
  - Used 18 genetic variants previously identified to be associated with T2D for Genetic Risk Score (GRS)
  - With no adjustment,  $C = 0.534$  and with GRS,  $C = 0.581$
  - Adjusting for age, sex, family history, body-mass index, fasting glucose level, systolic blood pressure, high-density lipoprotein cholesterol level, and triglyceride level,  $C = 0.900$ ; adding GRS,  $C = 0.901$
  - GRS resulted in appropriate reclassification of at most 4% of subjects
  - GRS predicted T2D, but provided only slightly better than common risk factors.