# Comment on "A proteomic surrogate for cardiovascular outcomes that is sensitive to multiple mechanisms of change in risk"

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**OVERLINE:  CARDIOVASCULAR DISEASE**

**Abstract:** The 27-protein model predicts cardiovascular disease but the applicability in clinical decision making remains unclear.

In a Science Translational Medicine paper by Williams *et al*. (*1*), the authors measured about 5000 plasma proteins in patients from nine clinical studies and constructed a 27-protein model for prediction of 4-year cardiovascular disease (CVD) outcomes, such as death and hospitalization for heart failure, myocardial infarction and stroke. The 27 proteins encompass 10 biological systems relevant to vascular pathology, and they can be easily measured from a single sample of plasma or serum. The C-statistic of 0.71 (95% CI 0.69–0.72) for the 27-protein model exceeded that of a traditional clinical model for 4-year prognosis with a C-statistic of 0.62 (0.60–0.63). Observed event rates were 5.6% for those assigned to a group with "low" predicted risk (0-7.5%), 11.2% for those assigned to "low-medium" predicted risk (7.6-25%), 20.0% for those in the "medium-high" predicted risk (26%-50%) and 43.4% for those assigned to a "high" predicted risk (51%-100%) category. The authors suggested that the model may provide a mechanistically universal surrogate endpoint for monitoring the benefits of cardioprotective therapies and an improvement in cost-effectiveness of care compared to current practice (*1*). In this technical comment, we highlight two translational issues related to the 27-protein score: prediction of a first (incident) CVD event, and applicability to clinical decision-making.

The most important clinical application and utility of a new prediction approach involves a CVD-free population in the primary prevention setting. Patients with pre-existing CVD are

supposed to be aggressively managed to prevent recurrent events, and the clinical value of risk prediction at this stage is less clear. For a prediction model to aid clinical decision making, three important, but often unreported measures of performance are (i) the detection rate, which denotes the proportion of test-positive individuals among people who developed the disease at follow-up; (ii) the false positive rate, or the proportion of individuals with a positive test result among those who did not develop the disease on follow up; and (iii) the ratio of true to false positives, also referred to as the odds of being affected given a positive result (OAPR), which can be calculated using the detection and false positive rate as well as information on disease incidence over a specified time (2).

Because CVD incidence and these three metrics were not considered by Williams *et al* (1), we performed a replication analysis in an independent dataset, the Whitehall cohort study (3), including assessment of C-statistics, calibration, detection and false positive rates, and the ratio of true to false positives for prediction of incident CVD (statistical code is available at DOI: 10.5281/zenodo.7071978). A flowchart of sample selection is shown in **fig. S1**. The cohort included 5,277 British adults with the same 27 plasma proteins analysed using the same SomaScan assay platform (SomaLogic, Inc.) as in Williams *et al*. (1, 4). Of the Whitehall study participants, 3,744 (70.9%) were men and 4,868 (92.2%) were of white ethnicity. Clinical characteristics at the time of blood collection for protein analysis are shown in **Table S1.** None of the participants had CVD at baseline and the baseline risk profile of the cohort was more favourable than that of the study by Williams *et al* which included populations with established CVD or other morbidities, such as heart failure, and suspicion of chronic coronary syndromes as well as elderly participants without known disease (1).

Using an identical CVD endpoint definition (myocardial infarction, stroke, heart failure hospitalization or all-cause death) and the 27-protein score as were used in the multicohort study by Williams *et al* (1), we observed 285 incident cases over a 10-year follow-up (incidence 5.4%). The distribution of the 27-protein score was less left-skewed in incident cases than non-cases with the former group having on average higher scores (median 9.7 vs 5.5) (**Fig. 1A**). The separation of cumulative hazard curves for CVD incidence by the 27-protein score quintiles increased during the entire follow-up; the hazard ratio was 5.34-fold (95% CI 3.56–8.02) in the top versus bottom quintile (**Fig. 1B**). The C-index, net reclassification index and calibration were comparable to those reported for the multicohort study by Williams *et al* (1) (**Fig. 1C**). Adding the 27-protein score to current predictive algorithms improved their C-index (5,6): for the American Heart Association/American College of Cardiology Atherosclerotic Cardiovascular Disease (ASCVD) calculator from 0.73 (95% CI 0.69–0.76) to 0.76 (95% CI 0.74–0.79) and for the UK QRISK3 algorithm from 0.75 (95% CI 0.72–0.78) to 0.78 (95% CI 0.75–0.81).

However, analyses employing the three metrics relevant for clinical decision-making illustrate the limitation of the 27-protein model in prediction of incident CVD **(Fig. 1D)**. At an estimated 10-year risk cut-off of 7.5% (used as the threshold for initiation of statin treatment according to US guidelines) a positive test detected 63% of incident cases (and missed 37% of the cases), with a 31% false positive rate. The OAPR was 1-to-8.7. The false positive rate decreased if a higher cut-off for positive test result was used. It was 3% for a 10-year CVD risk cut-off of 20% but then the test detected only 10% of incident cases and missed 90%. The corresponding OAPR was 1-to-3.9. The detection and false positive rates using 10-year CVD risk

cut-offs between these two extremes were 49% and 18% for a 10% cut-off and 26% and 7% for a 15% cut-off.

To examine whether these results are comparable to those for CVD risk scores used in clinical practice, we repeated the analysis after replacing the 27-protein model with the ASCVD calculator. The findings were very similar: detection and false positive rates were 67% and 33% (OAPR 1-to-8.6) for 10-year CVD risk cut-off of 7.5%. The corresponding rates were 10% and 2% (OAPR 1-to-4.2) for cut-off 20%. The performance of the 27-protein model was also in agreement with that previously reported for the QRISK algorithm (detection and false positive rates 40% and 13% for men and 26% and 6% for women) (2). By contrast, recommended screening tools, such as mammography for breast cancer (75% detection rate for an 8% false positive rate) and faecal immunochemical test (FIT, 79% detection rate for a 6% false positive rate) have much better performance (2).

A limitation is that Whitehall study participants were all in employment at recruitment and are healthier than the general population, both in terms of risk factor profiles and incidence of CVD. However, the associations between risk factors and CVD are not necessarily affected. A previous study showed that the association between established cardiovascular risk factors and risk of CVD in the Whitehall study was similar to that in general population studies (7). Another limitation is the relatively short follow-up. Some participants with false positive results may develop CVD after the 10-year period, although this is also possible for those with a 'true negative' result; the first would lead to an improvement and the latter to a worsening of predictive metrics.

In the light of the current evidence, the 27-protein model provides a predictive algorithm that may capture a wide range of biological processes and be a more sensitive index of the evolution of vascular pathology than the currently used cardiovascular risk models. In terms of C-statistics and calibration, the 27-protein model had similar performance in predicting a first cardiovascular event in our primary prevention study as in predicting the outcome of cardiovascular disease in the high-risk multicohort study by Williams et al, which included participants with varying morbidities (1). Similarly, the screening performance for 10-year risk of incident cardiovascular disease did not differ between the 27-protein model and the widely used ASCVD and QRISK3.

However, our finding that the odds of people developing cardiovascular disease among test positives was 1-to-4 to 1-to-9 (**Fig. 1E**) illustrates that the prediction of CVD with established clinical scores but also the 27-protein model remains challenging. With inexpensive, safe preventative interventions like statins, the direction of travel in cardiovascular prevention is toward widening eligibility for their use through progressive reductions in the threshold risk for intervention, such that statins are now prescribed on a population scale (8). Should any new drugs come to market with an intended use in primary prevention, their initially high cost (until patent expiry) and uncertainty on long-term safety are likely to necessitate targeting to those at very high risk with the best available risk tools. For new predictive biomarkers to take on the role of risk prediction, they will need to outperform or add to prediction offered by established risk models, which remains a high bar. None of this detracts from the insights such markers might provide into CVD biology or even as targets for new drug therapies.

In conclusion, the use of the established metrics of screening performance – detection at specific false positive rates and ratios of true to false positives – is needed to better evaluate

and display the predictive performance of new proteomics biomarkers. Without these, the translational value of such models in clinical populations will remain insufficiently characterised.

**List of SUPPLEMENTARY MATERIALS**
Materials and Methods
Fig S1
Table S1
Statistical code for analyses

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**FIGURE LEGEND**

**Fig. 1. 27-protein model as a predictor of 10-year risk of incident cardiovascular disease**. (**A**) The distribution of the 27-protein score among incident cardiovascular disease (CVD) cases and non-cases in the Whitehall study is shown. (**B**) Cumulative hazards curves for incident CVD by quintiles of the 27-protein score in Whitehall. (**C**) A comparison of the predictive performance of the 27-protein model between the Whitehall study on incident CVD (primary prevention) and the multicohort study by Williams *et al* (*1*) on CVD outcome. (**D**) The detection rate, false positive rate and the ratio of true to false positives for the 27-protein and ASCVD scores with various thresholds of a positive test result in the Whitehall study are shown. (**E**) An illustration of the findings for the 27-protein score based on two alternative widely used cut-offs for a test positive result (estimated 7.5% and 20% cardiovascular disease risk). ASCVD, atherosclerotic cardiovascular disease risk score; CVD, cardiovascular disease.

**A**



**B**

**C**
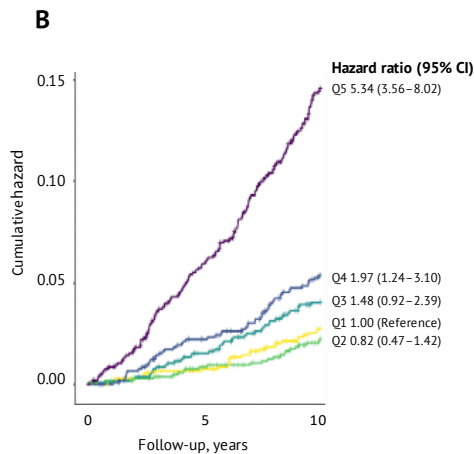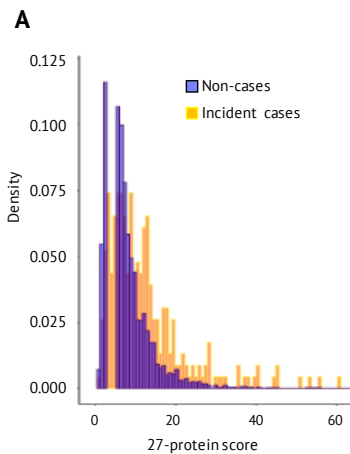
| | Whitehall | Williams et al (1) |
|---|---|---|
| | (10-y CVD risk) | (4-y CVD outcome) |
| **C-index** | | |
| 27-proteins only | 0.70 (0.67–0.73) | 0.71 (0.69–0.72) |
| ASCVD only | 0.73 (0.69–0.76) | 0.64 (0.62–0.65) |
| 27-proteins and ASCVD | 0.76 (0.74–0.79) | 0.73 (0.71–0.74) |
| Difference* | 0.07 (0.04–0.09) | 0.01 |
| | | |
| **NRI** | | |
| Continous NRI | 0.69 (0.57–0.80) | 0.43 |
| Reclassification in cases | 0.24 (0.14–0.32) | – |
| Reclassification in controls | 0.46 (0.41–0.49) | – |
| | | |
| **Category specific event rates** | | |
| 0–7.5% | 3.0 | 5.6 |
| 7.6–25% | 9.2 | 11.2 |
| 26–50% | 25.8 | 20.0 |
| 51–100% | – | 43.4 |

*Benefit of adding ASCVD score to the 27-protein model.
ASCVD, atherosclerotic cardiovascular disease risk score (a modified model was used in 4-year CVD prediction); CVD, cardiovascular disease; NRI, net reclassification

**D**

| Risk threshold | Screening metrics | 27-protein score | | | ASCVD score | | |
|---|---|---|---|---|---|---|---|
| | | No CVD | CVD | Metrics | No CVD | CVD | Metrics |
| Test neg: 0-7.5% | | 3432 | 106 | | 3343 | 93 | |
| Test pos: 7.5-100% | | 1560 | 179 | | 1649 | 192 | |
| | Detection rate | | | 0.63 | | | 0.67 |
| | False positive rate | | | 0.31 | | | 0.33 |
| | Ratio of true to false positives | | | 1 : 8.7 | | | 1 : 8.6 |
| | | | | | | | |
| Test neg: 0-10% | | 4095 | 146 | | 3942 | 134 | |
| Test pos: 10-100% | | 897 | 139 | | 1050 | 151 | |
| | Detection rate | | | 0.49 | | | 0.53 |
| | False positive rate | | | 0.18 | | | 0.21 |
| | Ratio of true to false positives | | | 1 : 6.5 | | | 1 : 7.0 |
| | | | | | | | |
| Test neg: 0-15% | | 4661 | 212 | | 4611 | 213 | |
| Test pos: 15-100% | | 331 | 73 | | 381 | 72 | |
| | Detection rate | | | 0.26 | | | 0.25 |
| | False positive rate | | | 0.07 | | | 0.08 |
| | Ratio of true to false positives | | | 1 : 4.5 | | | 1 : 5.3 |
| | | | | | | | |
| Test neg: 0-20% | | 4832 | 244 | | 4869 | 256 | |
| Test pos: 20-100% | | 160 | 41 | | 123 | 29 | |
| | Detection rate | | | 0.14 | | | 0.10 |
| | False positive rate | | | 0.03 | | | 0.02 |
| | Ratio of true to false positives | | | 1 : 3.9 | | | 1 : 4.2 |

**E**
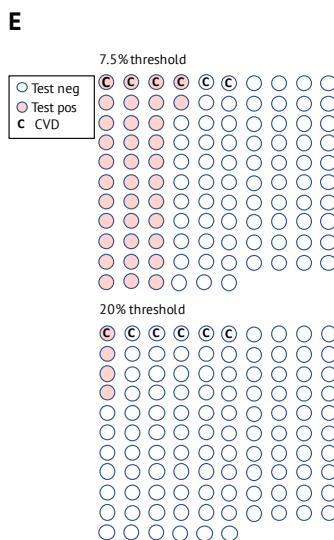
# Supplementary Materials for


**Comment on "A proteomic predictor of cardiovascular outcomes sensitive to diverse mechanisms of change in risk"**

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**The PDF file includes:**

> Materials and Methods
> Fig S1
> Table S1
> Statistical code

**Other Supplementary Material for this manuscript includes the following:**

> MDAR Reproducibility Checklist

**Materials and Methods**

We used data from the British Whitehall II study used for analysis. The Whitehall II study is a prospective cohort study that was established among 10,308 British civil servants (33.1% women, age range 35–55) in 1985–1988. Since baseline, follow-up clinical data collection waves have taken place every 4–5 years with each wave lasting about 2 years, with the last wave conducted in 2015–2016. In addition to clinical examinations in the study, data over the follow-up have been obtained via linkage to electronic health records of the UK National Health Service (NHS) for participants recruited to the study. The NHS provides most of the health care in the country, including in- and out-patient care, and record linkage is undertaken using a unique NHS identifier held by all UK residents. Data from linked records have been updated on an annual basis, until 31st March 2019.

Written, informed consent from participants was obtained at each contact. Research ethics approvals were renewed at each wave; the most recent approval was obtained from the University College London Hospital Committee on the Ethics of Human Research (reference number 85/0938).

Sample selection for the present analysis is described in **Fig. S1** and clinical characteristics of the study participants are presented in **Table S1**.

Statistical analyses were performed using Stata MP (version 16) and included C-statistics, calibration, detection and false positive rates, and the ratio of true to false positives for prediction of incident CVD (**statistical code** is provided on p. 3–7). To evaluate the score's ability to aid clinical decision making, we dichotomized the score into 'test positive' versus 'test negative' using alternative cut-offs. For positive test cases, we calculated detection rate (the proportion of incident dementia in cases who were test positive, also known as sensitivity), false positive rate (the proportion of test positive cases who were not diagnosed with dementia, which equals to 1 - specificity), and the ratio of true to false positives (also referred to as the odds of being affected given a positive result [OAPR]). The formulas were as follows:

$$Detection\ rate = a/(a+c),$$
$$False\ positive\ rate = b/(b+d),$$
$$Ratio\ of\ true\ to\ false\ positives = a/b,$$

where a, b, c and d represent different combinations of risk scores and CVD caseness as defined below:

| Risk score | **Incident CVD during the follow-up** | |
| --- | --- | --- |
| | Yes | No |
| Test positive | a | b |
| Test negative | c | d |

```
┌─────────────────────────────────────────────┐
│ 10308 Participants in Whitehall study cohort │
│               in 1985–1988                   │
└─────────────────────────────────────────────┘
                     │
                     │──────────────────────────▶ ┌──────────────────────────────┐
                     │                             │      2440 Did not attend       │
                     │                             │ clinical examination in 1997–1999 │
                     ▼                             └──────────────────────────────┘
┌─────────────────────────────────────────────┐
│ 7868 Participated in clinical examination and │
│      questionnaire survey in 1997–1999        │
└─────────────────────────────────────────────┘
                     │
                     │──────────────────────────▶ ┌──────────────────────────────┐
                     │                             │     1539 Refused a blood draw  │
                     ▼                             └──────────────────────────────┘
┌─────────────────────────────────────────────┐
│ 6329 Were tested for 27 proteins using SomaScan │
└─────────────────────────────────────────────┘
                     │
                     │──────────────────────────▶ ┌──────────────────────────────┐
                     │                             │     44 Were excluded due to    │
                     │                             │   low-quality protein assessment │
                     ▼                             └──────────────────────────────┘
┌─────────────────────────────────────────────┐
│ 6285 Protein assessment passed quality control │
└─────────────────────────────────────────────┘
                     │
                     │──────────────────────────▶ ┌──────────────────────────────┐
                     │                             │     892 Were excluded due to   │
                     │                             │      missing clinical data     │
                     ▼                             └──────────────────────────────┘
┌─────────────────────────────────────────────┐
│ 5393 Had no missing data on proteins or       │
│             clinical variables                │
└─────────────────────────────────────────────┘
                     │
                     │──────────────────────────▶ ┌──────────────────────────────┐
                     │                             │     116 Were excluded due to   │
                     │                             │  prevalent cardiovascular disease │
                     ▼                             └──────────────────────────────┘
┌─────────────────────────────────────────────┐
│ 5277 Were included in the analytic sample of  │
│  cardiovascular disease-free participants     │
└─────────────────────────────────────────────┘
```

**Fig. S1. Flow chart for sample selection.**

**Table S1. Clinical characteristics of the included participants**

| Characteristic | Statistics |
|---|---:|
| Total cohort, N | 5277 |
| 27-protein score, mean (SD) | 7.3 (6.0) |
| ASCVD Risk Estimator, mean (SD) | 6.8 (5.5) |
| QRISK3 Risk Prediction Algorithm, mean (SD) | 8.3 (5.9) |
| Age, mean (SD) | 55.8 (6.0) |
| White ethnicity, N (%) | 4,868 (92.2) |
| Men, N (%) | 3,744 (70.9) |
| Systolic blood pressure mmHg, mean, (SD) | 124 (17) |
| Antihypertensive medication, N (%) | 620 (11.7) |
| Total cholesterol mmol/l, mean (SD) | 6.0 (1.1) |
| HDL-cholesterol mmol/l, mean, (SD) | 1.5 (0.4) |
| Smoking, N (%) | 495 (9.4) |
| Prevalent diabetes, N (%) | 173 (3.3) |
| Prevalent cardiovascular disease, N (%) | 0 (0.0) |
| Incident cardiovascular events in 10-year follow-up, N (%) | 285 (5.4) |

ASCVD, Atherosclerotic cardiovascular disease; SD, standard deviation.

**Statistical code:**

Statistical code used in the study can be found at Zenodo (DOI: 10.5281/zenodo.7071978) and below:

```
# Load data

whii_data <- read.dta("Whitehall_II_dataset.dta")

# Create the protein score

whii_data = whii_data %>% mutate (protein_risk = exp(-(2.83 +
                              -0.09 * seq.8323.163 +
                              -0.23 * seq.16751.15 +
                              -0.05 * seq.11109.56 +
                               0.01 * seq.2765.4 +
                              -0.02 * seq.9266.1 +
                               0.09 * seq.9793.145 +
                              -0.03 * seq.6544.33 +
                              -0.14 * seq.4496.60 +
                               0.02 * seq.3175.51 +
                              -0.03 * seq.2652.15 +
                               0.13 * seq.8841.65 +
                               0.02 * seq.6927.7 +
                              -0.01 * seq.4297.62 +
                               0.14 * seq.15559.5 +
                               0.04 * seq.8250.2 +
                              -0.07 * seq.15472.16 +
                              -0.07 * seq.5443.62 +
                              -0.07 * seq.2997.8 +
                               0.08 * seq.5030.52 +
                              -0.11 * seq.15565.102 +
                               0.1 * seq.8885.6 +
                               0.03 * seq.9326.33 +
                               0.11 * seq.2617.56 +
                              -0.1 * seq.8983.7 +
                              -0.08 * seq.17706.4 +
                               0.22 * seq.12433.8 +
                               0.1 * seq.4498.62)
                           )
                )

# Plot protein score distribution in cases and non-cases

data_ctrl = whii_data %>% filter(outcome_indicator==0)
data_case = whii_data %>% filter(outcome_indicator==1)

data_ctrl$ind <- 'ctrl'
data_case$ind <- 'case'

data_comb <- rbind(data_ctrl, data_case)

ggplot(data_case, aes(protein_risk, fill = outcome_indicator)) + geom_density(alpha = 0.2)
```

```
ggplot(data_comb, aes(protein_risk, fill = ind)) +
  geom_histogram(alpha = 0.5, aes(y = ..density..), position = 'identity', bins = 100) +
  theme(panel.background = element_rect(fill = 'white', colour = 'white'),
        axis.line = element_line(colour = "black"),
        legend.position = "none",
        axis.text=element_text(size=20),
        axis.title=element_text(size=20)) +
  xlab("Protein score") +
  ylab("Density") +
  xlim(0, 80) +
  ylim(0, 0.12)

# Create quintiles and cumulative hazard plot

surv_object <- Surv(time = whii_data$eof, event = whii_data$outcome_indicator)
surv_object

whii_data = whii_data %>%
  mutate(protein_risk_cat = ntile(row_number(protein_risk), 5)
  )

fit <- survfit(surv_object ~ protein_risk_cat, data = whii_data)
summary(fit)

ggsurvplot(fit, data = whii_data,  ylim = c(0, 0.20), xlab = "Time in years",
       fun = "cumhaz",
       legend.title = "Quintiles",
       legend.labs = c("1", "2", "3", "4", "5"))

# Category specific event rates

whii_data$protein_risk_cut_7.5 = cut(whii_data$protein_risk, breaks = c(0, 7.5, 100))
whii_data$protein_risk_cut_10 = cut(whii_data$protein_risk, breaks = c(0, 10, 100))
whii_data$protein_risk_cut_15 = cut(whii_data$protein_risk, breaks = c(0, 15, 100))
whii_data$protein_risk_cut_20 = cut(whii_data$protein_risk, breaks = c(0, 20, 100))
whii_data$protein_risk_cut_25 = cut(whii_data$protein_risk, breaks = c(0, 25, 100))

table(whii_data$protein_risk_cut_7.5, whii_data$outcome_indicator)
table(whii_data$protein_risk_cut_10, whii_data$outcome_indicator)
table(whii_data$protein_risk_cut_15, whii_data$outcome_indicator)
table(whii_data$protein_risk_cut_20, whii_data$outcome_indicator)
table(whii_data$protein_risk_cut_25, whii_data$outcome_indicator)

whii_data$ascvd_risk_cut_7.5 = cut(whii_data$ascvd_risk, breaks = c(0, 7.5, 100))
whii_data$ascvd_risk_cut_10 = cut(whii_data$ascvd_risk, breaks = c(0, 10, 100))
whii_data$ascvd_risk_cut_15 = cut(whii_data$ascvd_risk, breaks = c(0, 15, 100))
whii_data$ascvd_risk_cut_20 = cut(whii_data$ascvd_risk, breaks = c(0, 20, 100))
whii_data$ascvd_risk_cut_25 = cut(whii_data$ascvd_risk, breaks = c(0, 25, 100))

table(whii_data$ascvd_risk_cut_7.5, whii_data$outcome_indicator)
table(whii_data$ascvd_risk_cut_10, whii_data$outcome_indicator)
table(whii_data$ascvd_risk_cut_15, whii_data$outcome_indicator)
```

```
table(whii_data$ascvd_risk_cut_20, whii_data$outcome_indicator)
table(whii_data$ascvd_risk_cut_25, whii_data$outcome_indicator)

# Protein model

res.prot = cph(formula=Surv(eof, outcome_indicator) ~ protein_risk ,
        data=whii_data, x=TRUE, y=TRUE, surv = TRUE, time.inc = 10)
res.prot

C_index_prot = concordance(res.prot)
C_index_prot

C_index_prot_cis = c(C_index_prot$concordance, (C_index_prot$concordance)-1.96*(sqrt(C_index_prot$var)),
(C_index_prot$concordance)+1.96*(sqrt(C_index_prot$var)))
C_index_prot_cis

str(C_index_prot)
C_index_prot$concordance
C_index_prot$cvar
sqrt(C_index_prot$var)


# ASCVD model

res.ascvd = cph(formula=Surv(eof, outcome_indicator) ~ ascvd_risk ,
        data=whii_data, x=TRUE, y=TRUE, surv = TRUE, time.inc = 10)
res.ascvd
C_index_ascvd = concordance(res.ascvd)
C_index_ascvd

C_index_ascvd = c(C_index_ascvd$concordance, (C_index_ascvd$concordance)-1.96*(sqrt(C_index_ascvd$var)),
(C_index_ascvd$concordance)+1.96*(sqrt(C_index_ascvd$var)))
C_index_ascvd


# Combined model

res.comb = cph(formula=Surv(eof, outcome_indicator) ~ protein_risk + ascvd_risk ,
        data=whii_data, x=TRUE, y=TRUE, surv = TRUE, time.inc = 10)
res.comb
C_index_comb = concordance(res.comb)
C_index_comb

C_index_comb = c(C_index_comb$concordance, (C_index_comb$concordance)-1.96*(sqrt(C_index_comb$var)),
(C_index_comb$concordance)+1.96*(sqrt(C_index_comb$var)))
C_index_comb


# Difference in C-index between protein and combined model

models <- concordance(res.prot, res.comb)
models
```

```
contr = c(-1, 1)
d = contr %*% coef(models)
dvar = contr %*% vcov(models) %*% contr
difference = c(contrast=d, sd=sqrt(dvar), z=d/sqrt(dvar))
difference
str(difference)
difference[1]

difference_cis = c(difference[1], (difference[1])-1.96*(difference[2]), (difference[1])+1.96*(difference[2]))
difference_cis

# NRI

res.prot = (coxph(Surv(eof, outcome_indicator) ~ protein_risk, data=whii_data, x=TRUE))
res.comb = (coxph(Surv(eof, outcome_indicator) ~ protein_risk + ascvd_risk, data=whii_data, x=TRUE))

NRI = nricens(mdl.std = res.prot, mdl.new = res.comb,
                 updown = "diff", cut = 0, t0=10, niter=200)


# QRISK3 model

res.qrisk3 = cph(formula=Surv(eof, outcome_indicator) ~ qrisk3 ,
          data=whii_data, x=TRUE, y=TRUE, surv = TRUE, time.inc = 10)
res.qrisk3
C_index_qrisk3 = concordance(res.qrisk3)
C_index_qrisk3

C_index_qrisk3 = c(C_index_qrisk3$concordance, (C_index_qrisk3$concordance)-1.96*(sqrt(C_index_qrisk3$var)),
(C_index_qrisk3$concordance)+1.96*(sqrt(C_index_qrisk3$var)))
C_index_qrisk3


# Combined model

res.comb = cph(formula=Surv(eof, outcome_indicator) ~ protein_risk + qrisk3 ,
          data=whii_data, x=TRUE, y=TRUE, surv = TRUE, time.inc = 10)
res.comb
C_index_comb = concordance(res.comb)
C_index_comb

C_index_comb = c(C_index_comb$concordance, (C_index_comb$concordance)-1.96*(sqrt(C_index_comb$var)),
(C_index_comb$concordance)+1.96*(sqrt(C_index_comb$var)))
C_index_comb


# Difference in C-index between protein and combined model

models <- concordance(res.prot, res.comb)
models

contr = c(-1, 1)
d = contr %*% coef(models)
```

```
dvar = contr %*% vcov(models) %*% contr
difference = c(contrast=d, sd=sqrt(dvar), z=d/sqrt(dvar))
difference
str(difference)
difference[1]

difference_cis = c(difference[1], (difference[1])-1.96*(difference[2]), (difference[1])+1.96*(difference[2]))
difference_cis


# NRI

res.prot = (coxph(Surv(eof, outcome_indicator) ~ protein_risk, data=whii_data, x=TRUE))
res.comb = (coxph(Surv(eof, outcome_indicator) ~ protein_risk + qrisk3, data=whii_data, x=TRUE))

NRI = nricens(mdl.std = res.prot, mdl.new = res.comb,
        updown = "diff", cut = 0, t0=10, niter=200)
```