RISK PREDICTION MODELS FOR ENDOMETRIAL CANCER

DEVELOPMENT AND VALIDATION IN THE EPIDEMIOLOGY OF ENDOMETRIAL CANCER CONSORTIUM

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MOTIVATION.

4^{th} most commonly diagnosed cancer among women in US

Increasing incidence and mortality in the past decade

Increasing prevalence of major endometrial cancer risk factors (e.g., nulliparity)

Can we develop a risk prediction model to identify high-risk?

EXISTING PREDICTION MODELS FOR ENDOMETRIAL CANCER: PLCO TRIAL & NIH-AARP STUDY.

TRAINING DATA

- 146,679 women
- 1,559 incident cases

VALIDATION DATA

Nurses Health Study

- 37,241 women
- 532 incident cases

MODEL PREDICTORS

BMI, menopausal hormone therapy (MHT) use, parity, menopausal status, age at menopause, smoking status, oral contraceptive (OC) use, HMT × BMI interaction

RESULTS

AUC: 0.67

E/O ratio: 1.20

Pfeiffer et al., (PLOS Medicine, 2013)

EXISTING PREDICTION MODELS FOR ENDOMETRIAL CANCER: EPIC STUDY.

TRAINING DATA

- 201,811 women
- 855 incident cases

VALIDATION DATA

- Internally validated
- Five-fold cross validation

MODEL PREDICTORS

BMI, menopausal status, age at menarche and menopause, OC use, parity, age at first full-term pregnancy, duration of MHT use, smoking status, OC × BMI interaction

RESULTS

AUC: 0.77 (0.71 for age-only model)

E/O ratio: 0.99

Hüsing et al., (EJE, 2016)

CURRENT GAPS.

(1) Models were trained on selective study populations

- Limited generalizability

(2) Contributions of genetic factors have yet to be assessed

OBJECTIVES.

Develop a model that will predict an individual's 10-year risk for endometrial cancer based on epidemiologic questionnaire data.

Evaluate the model's performance

Assess the additive contribution of genetic factors to the model.

METHODS: MODEL DEVELOPMENT.

- Relative risk for predictors
- Marginal risks for endometrial cancer
- Marginal risks for competing events
- Risk factor distribution of underlying population

DATA:
E2C2

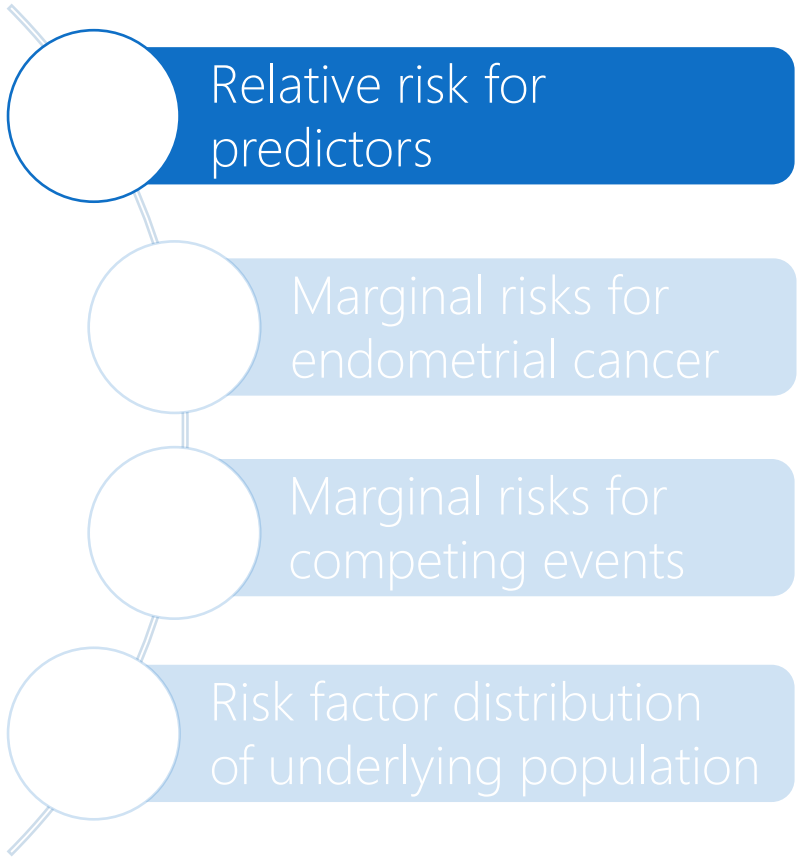
PREDICTORS

MODEL

E2C2 Consortium

- 19 case-control studies
- Postmenopausal, white, aged 45-85
- >6,000 cases and >9,000 controls

METHODS: MODEL DEVELOPMENT.



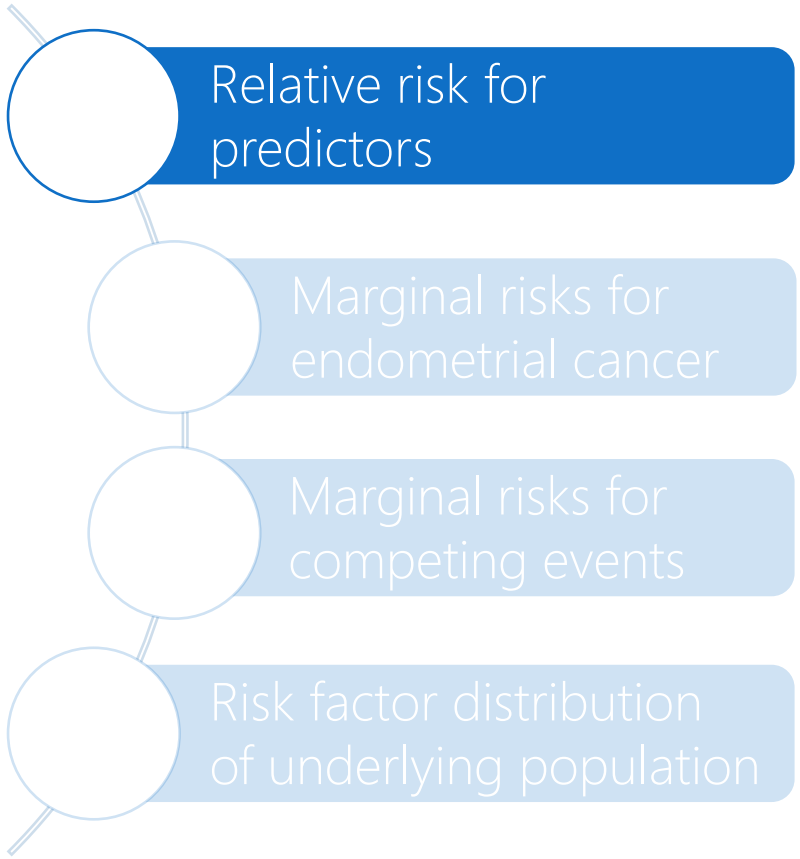
DATA: E2C2

PREDICTORS

MODEL

- Reproductive factors
  (e.g., age at menarche, age at first birth)
- Lifestyle factors
  (e.g., smoking, body mass index)
- Exogenous hormone-related factors
  (e.g., hormone therapy use)
- Medical history
  (e.g., diabetes, hypertension)
- Interaction terms
  (e.g., BMI×HT use, BMI×OC use)

METHODS: MODEL DEVELOPMENT.



DATA: E2C2

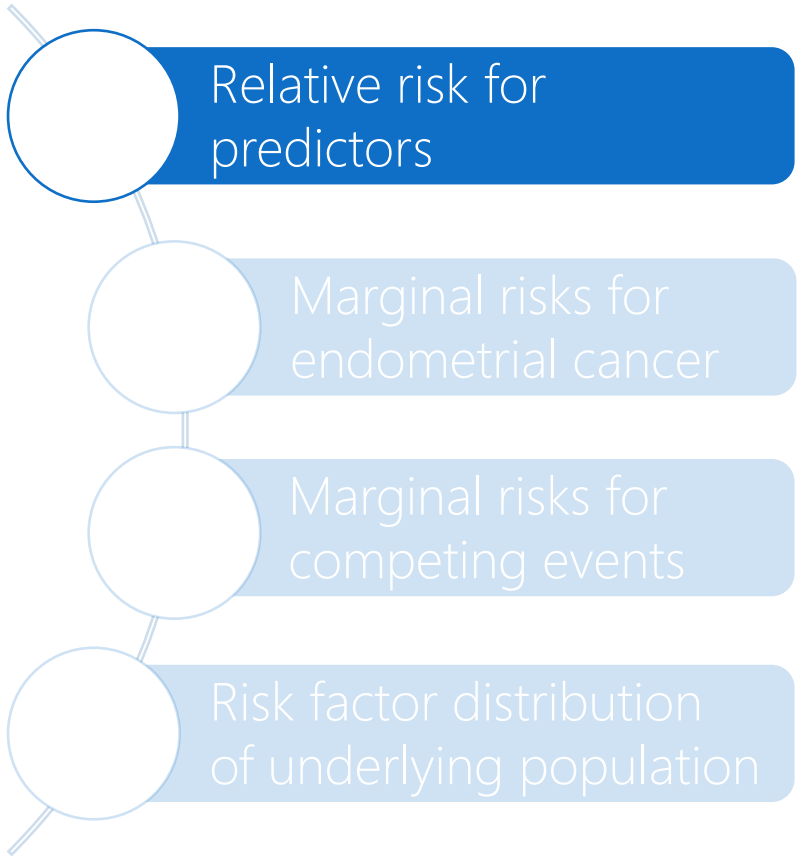
PREDICTORS

MODEL

Genetic variants

- 18 genome-wide significant single nucleotide polymorphisms (SNPs)
- From O'Mara et al. (Nature Communications, 2018)

METHODS: MODEL DEVELOPMENT.



DATA: E2C2

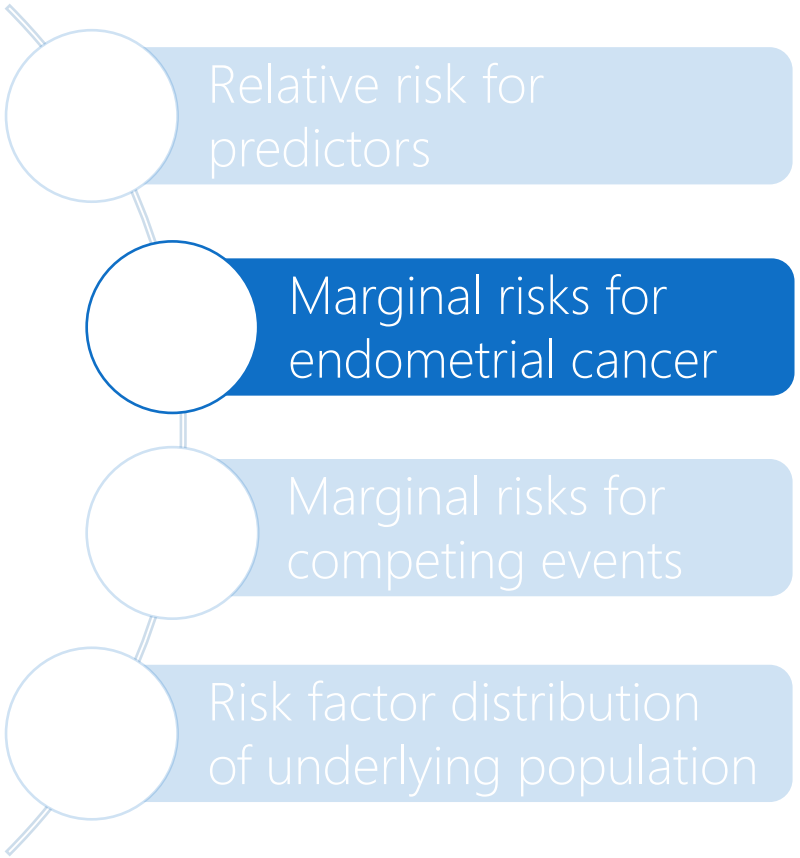
PREDICTORS

MODEL

Logistic group LASSO model for variable selection and regularization

- Age and study site forced into the model
- Remaining model parameters were subject to penalization
  - Larger penalty = fewer variables retained
  - Leave-one-study-out cross-validation to select tuning parameter

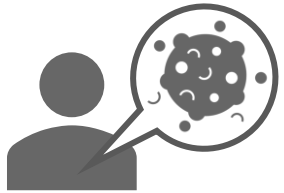
METHODS: MODEL DEVELOPMENT.



- Corrected for prevalence of hysterectomy
- Data source for endometrial cancer incidence: SEER
  - NHS: 1989-1993
  - PLCO: 1996-2000
  - NHS II: 2003-2007
- Data source for hysterectomy prevalence: BRFSS
  - NHS: 1988
  - PLCO: 1996-1998
  - NHS II: 2006 and 2008

METHODS: MODEL DEVELOPMENT.

- Relative risk for predictors
- Marginal risks for endometrial cancer
- **Marginal risks for competing events**
- Risk factor distribution of underlying population

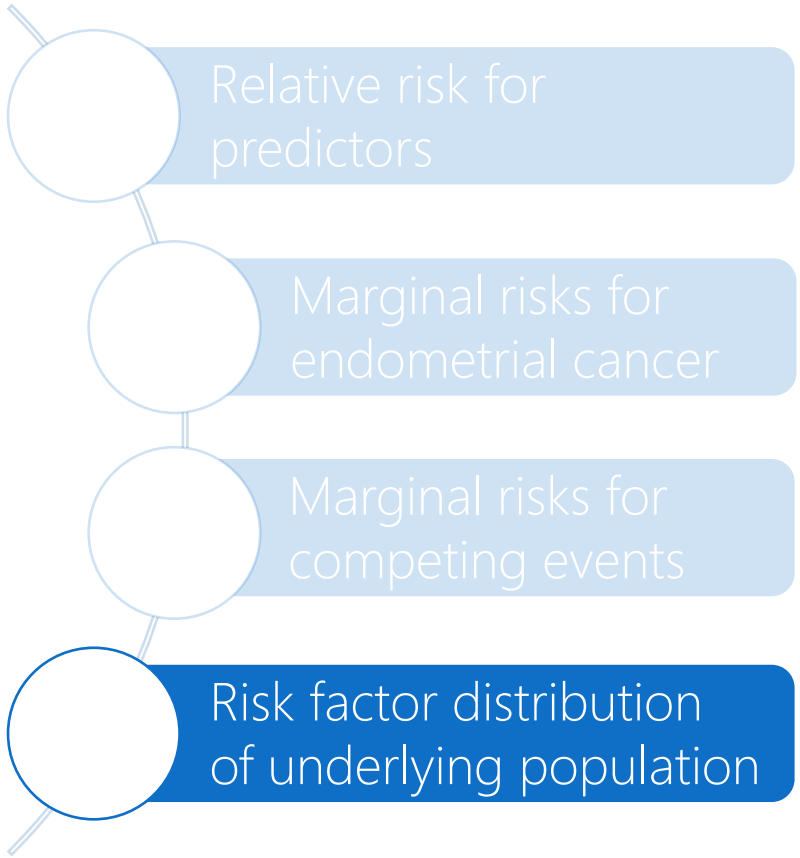


1) Hysterectomy: BRFSS

2) Other cancers: SEER
   - NHS: 1989-1993
   - PLCO: 1996-2000
   - NHS II: 2003-2007

3) Death: CDC WONDER
   - NHS: 1988
   - PLCO: 1997
   - NHS II: 2004

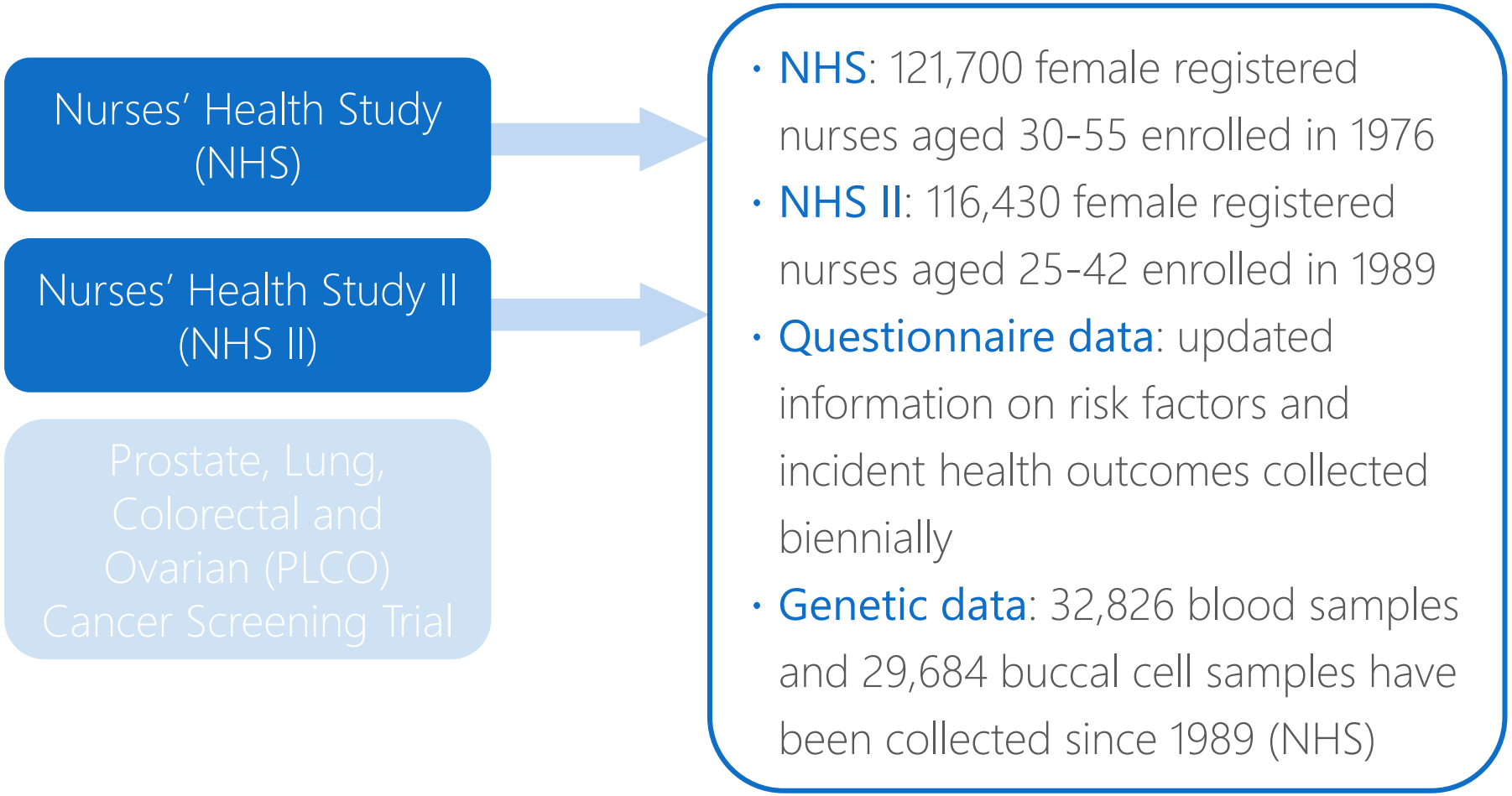
METHODS: MODEL DEVELOPMENT.



National Health and Nutrition Examination Survey (NHANES)

- NHS and PLCO: 1999-2000
- NHS II: 2007-2008

METHODS: MODEL VALIDATION DATA.



METHODS: MODEL VALIDATION DATA.

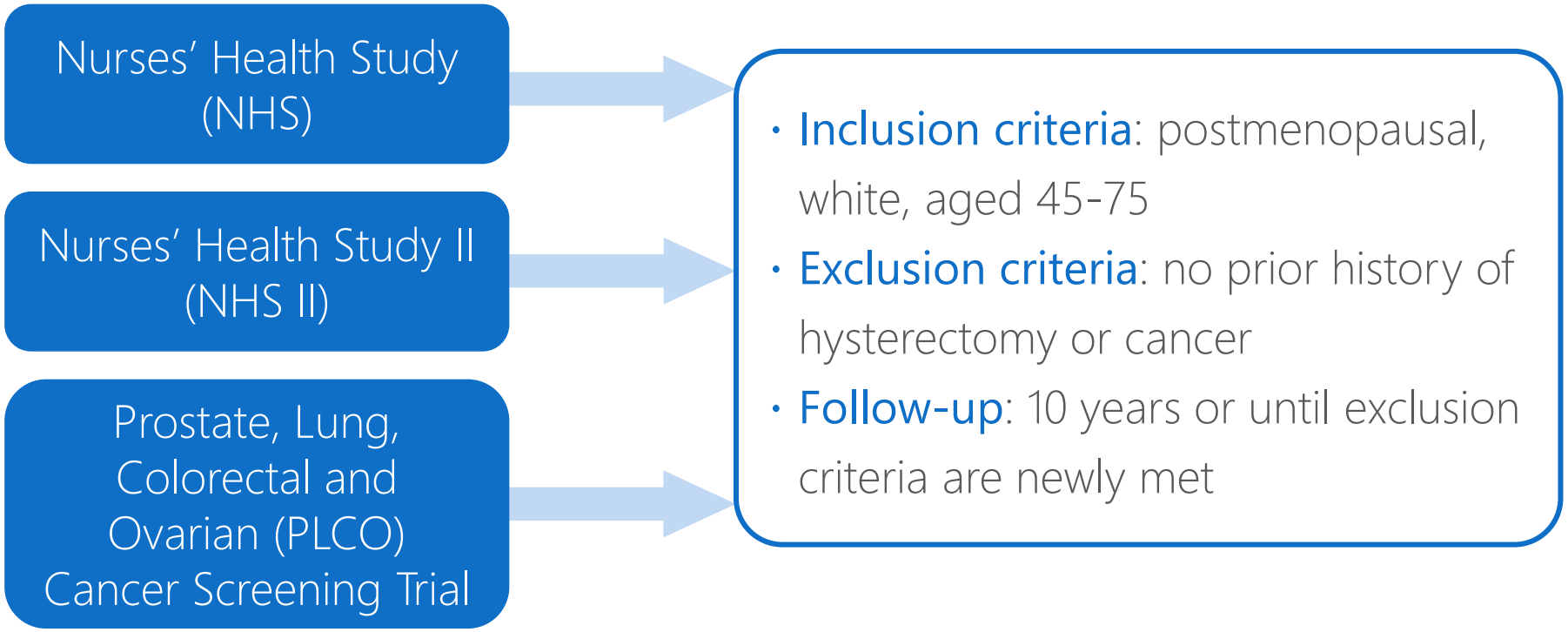
Nurses' Health Study (NHS)

Nurses' Health Study II (NHS II)

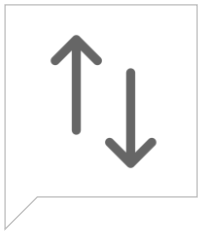
Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial

- **Population**: 78,232 women aged 55-74 years were enrolled between 1993 and 2001 across 10 screening centers
- **Questionnaire data**: baseline and supplemental questionnaire (2006)
- **Genetic data**: blood samples collected at enrollment and annual screening visits

METHODS: MODEL VALIDATION DATA.



METHODS: MODEL VALIDATION METRICS.

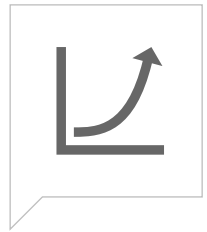


DISCRIMINATION

- Area under the receiver operating characteristic curve (AUC) based on 10-year risk

ABSOLUTE RISK CALIBRATION

- Expected-to-observed (E/O) ratio of 10-year absolute risk across deciles of risk
- Hosmer-Lemeshow χ^2 test



RELATIVE RISK CALIBRATION

- Goodness-of-fit test for predicted versus observed relative 10-year risk across deciles of risk

METHODS: ABSOLUTE RISK ESTIMATES IN MORE CURRENT POPULATION.

Combined:

- Relative risk estimates from group LASSO model
- Endometrial cancer incidence rates (SEER 2013-2017)
- Hysterectomy prevalence (BRFSS 2016 and 2018)
- Incidence rates for competing risks (2017 CDC WONDER data for mortality; 2013-2017 SEER data for other cancers)
- Risk factor distributions (NHANES 2017-2018)

RESULTS: MODEL PREDICTORS.

Characteristics	RR
Demographic factors	
Education, %	
High school or below	(ref)
Some college or equivalent	0.97
College or above	0.96
Lifestyle factors	
Smoking status, %	
Never smoker	(ref)
Former smoker	0.80
Current smoker	0.64
Body mass index (kg/m^2), %	
<18.5	0.74
18.5 to <25	(ref)
25 to <30	1.41
30 to <35	2.49
≥35	5.57

Characteristics	RR
Reproductive and hormonal factors	
Parity, %	
0	(ref)
1	1.10
2	0.91
3	0.77
≥4	0.60
Age at first birth, %	
<20	(ref)
20 to <25	0.96
25 to <30	0.85
30 to <35	0.83
≥35	0.84
Never given birth	1.28

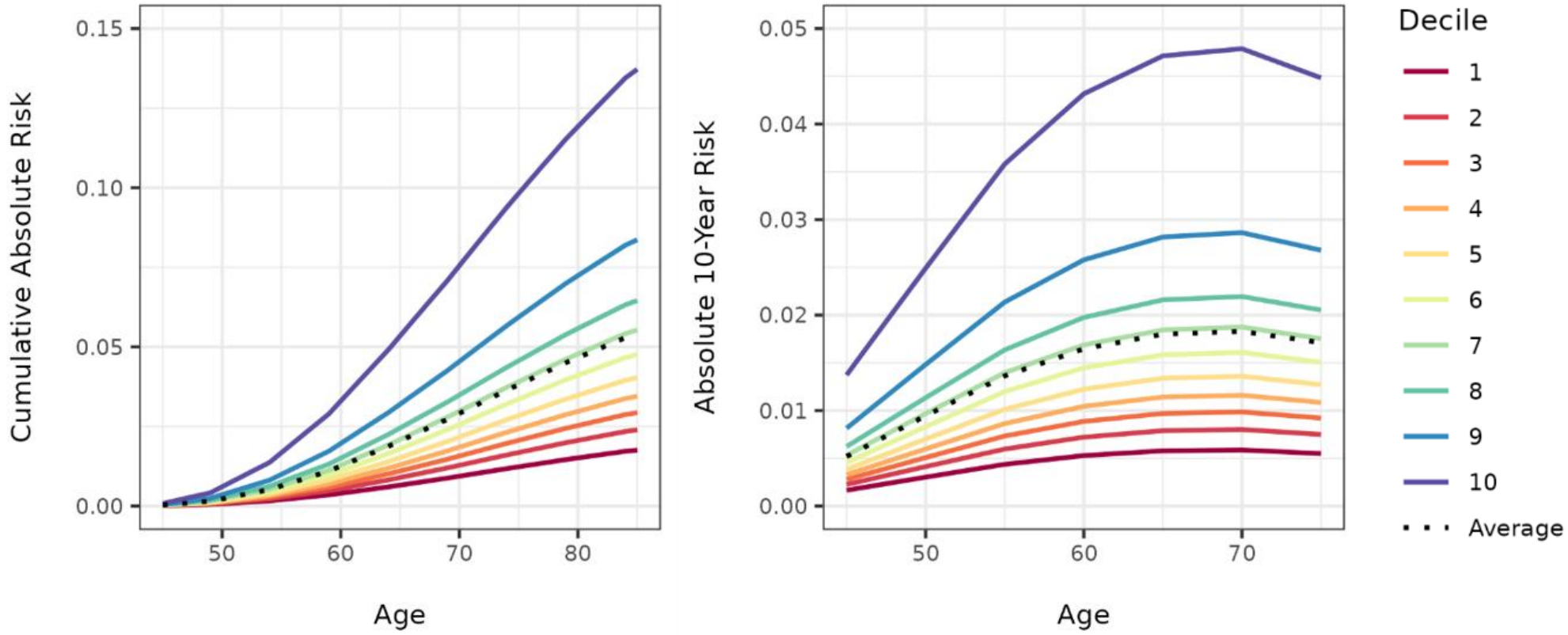
(cont.)

RESULTS: MODEL PREDICTORS.

Characteristics	RR
Reproductive and hormonal factors	
Age at menarche, %	
≤9	(ref)
10-11	1.04
12-13	1.04
14-15	0.92
≥16	0.89
Any HT use, %	1.61
Any E-only HT use, %	1.06
Duration of E-only HT use (years), %	
0	(ref)
>0 to 5	0.84
>5 to 10	1.42
>10	2.55
(cont.)	

Characteristics	RR
Reproductive and hormonal factors	
Any E+P HT use, %	0.82
Duration of E+P HT use (years), %	
0	(ref)
>0 to 5	1.00
>5 to 10	1.00
>10	1.00
Any OC use, %	0.79
Duration of OC use (years), %	
0	(ref)
>0 to 5	1.05
>5 to 10	0.94
>10	0.69
Clinical factors	
History of diabetes, n (%)	1.39
History of hypertension, n (%)	1.22

RESULTS: ESTIMATED CUMULATIVE AND 10-YEAR RISKS.



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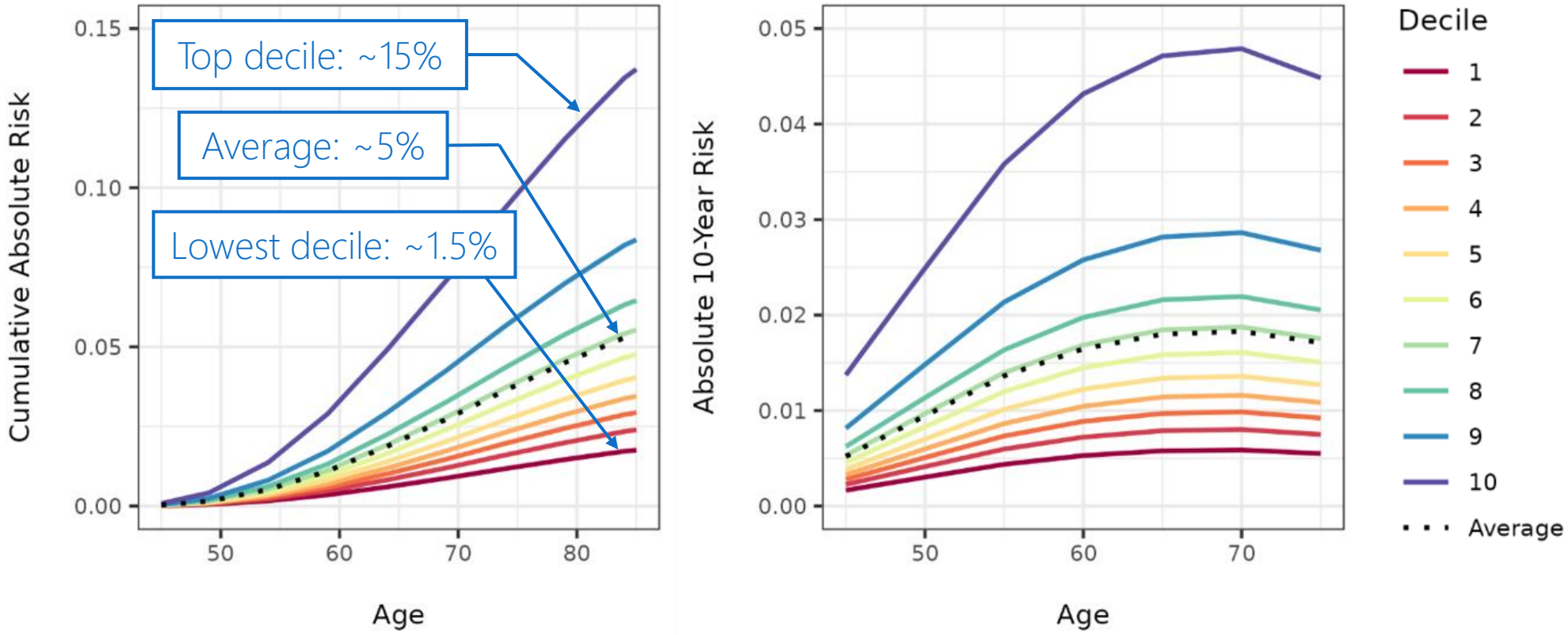


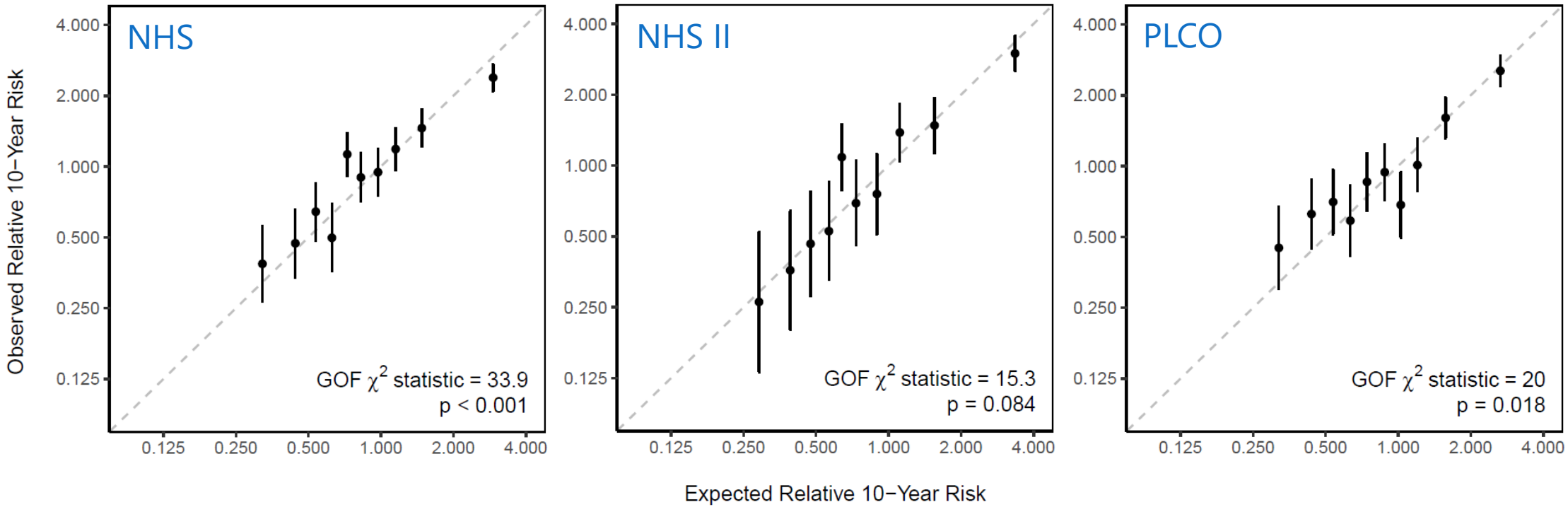
RESULTS: MODEL DISCRIMINATION (EPIDEMIOLOGIC MODEL).

VALIDATION COHORT	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	AUC (95% CI)
NHS	68,150	700	0.647 (0.626, 0.667)
NHS II	56,076	304	0.693 (0.664, 0.723)
PLCO	39,996	511	0.640 (0.615, 0.665)

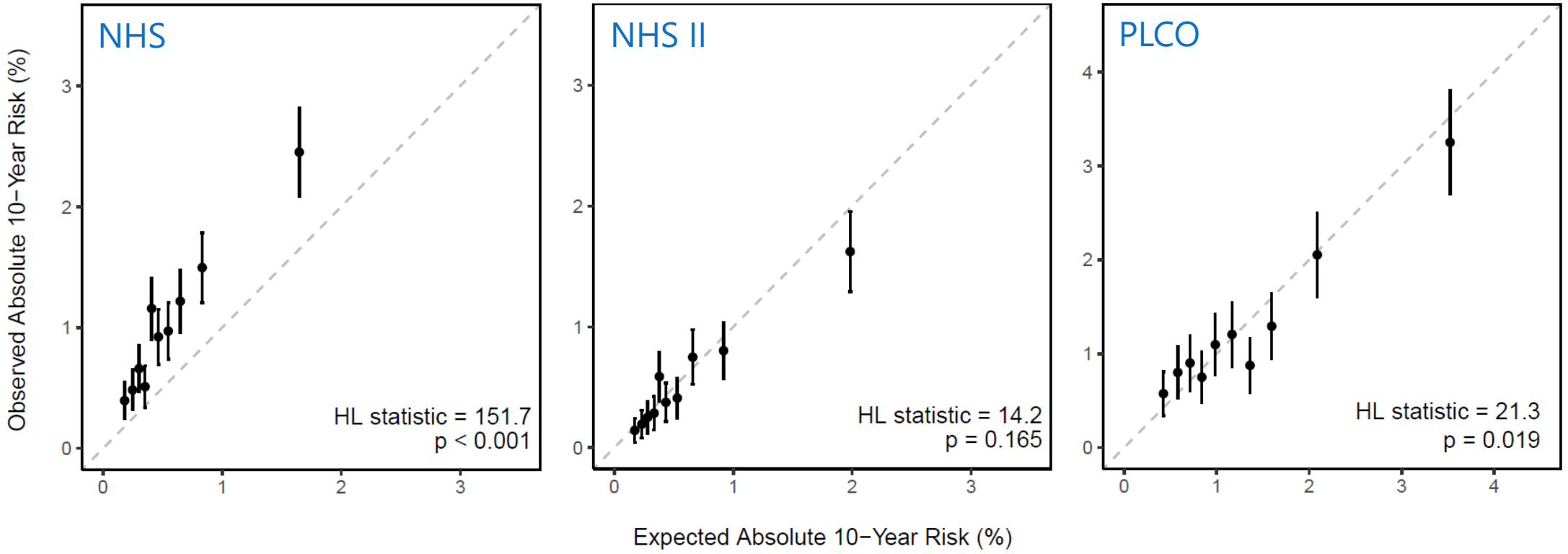
RESULTS: MODEL DISCRIMINATION (EPIDEMIOLOGIC + GENETIC MODEL).

VALIDATION COHORT	NUMBER OF PARTICIPANTS	NUMBER OF EVENTS	AUC (95% CI)	
			EPIDEMIOLOGIC MODEL	EPIDEMIOLOGIC + GENETIC MODEL
NHS (Genetic cohort)	11,365	166	0.613 (0.570, 0.656)	0.613 (0.570, 0.656)
PLCO (Genetic cohort)	30,102	401	0.635 (0.606, 0.664)	0.665 (0.636, 0.693)

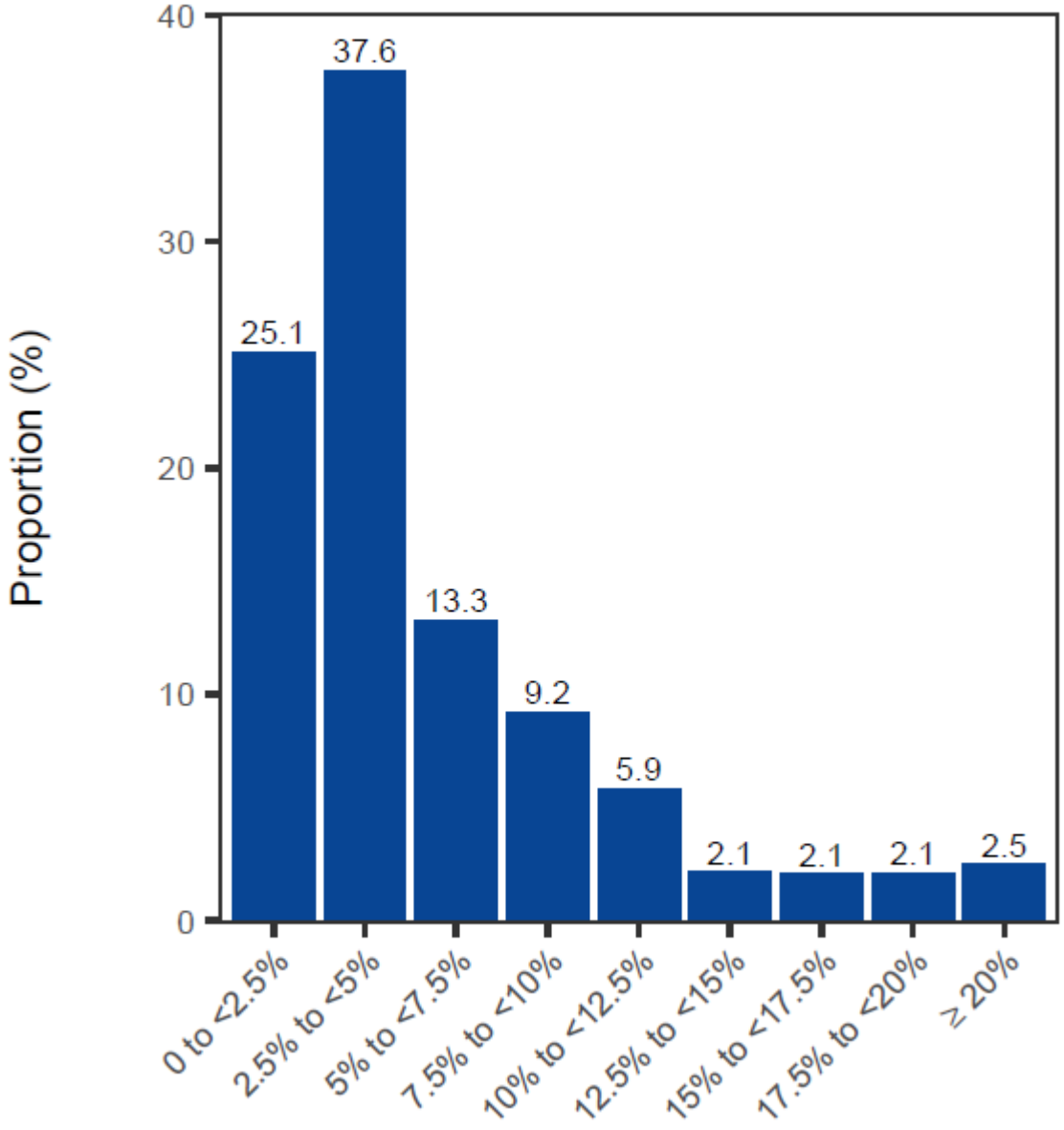
RESULTS: MODEL CALIBRATION OF RELATIVE RISKS.



RESULTS: MODEL CALIBRATION OF ABSOLUTE RISKS.



RESULTS: ESTIMATED RISKS IN A MORE CURRENT POPULATION.



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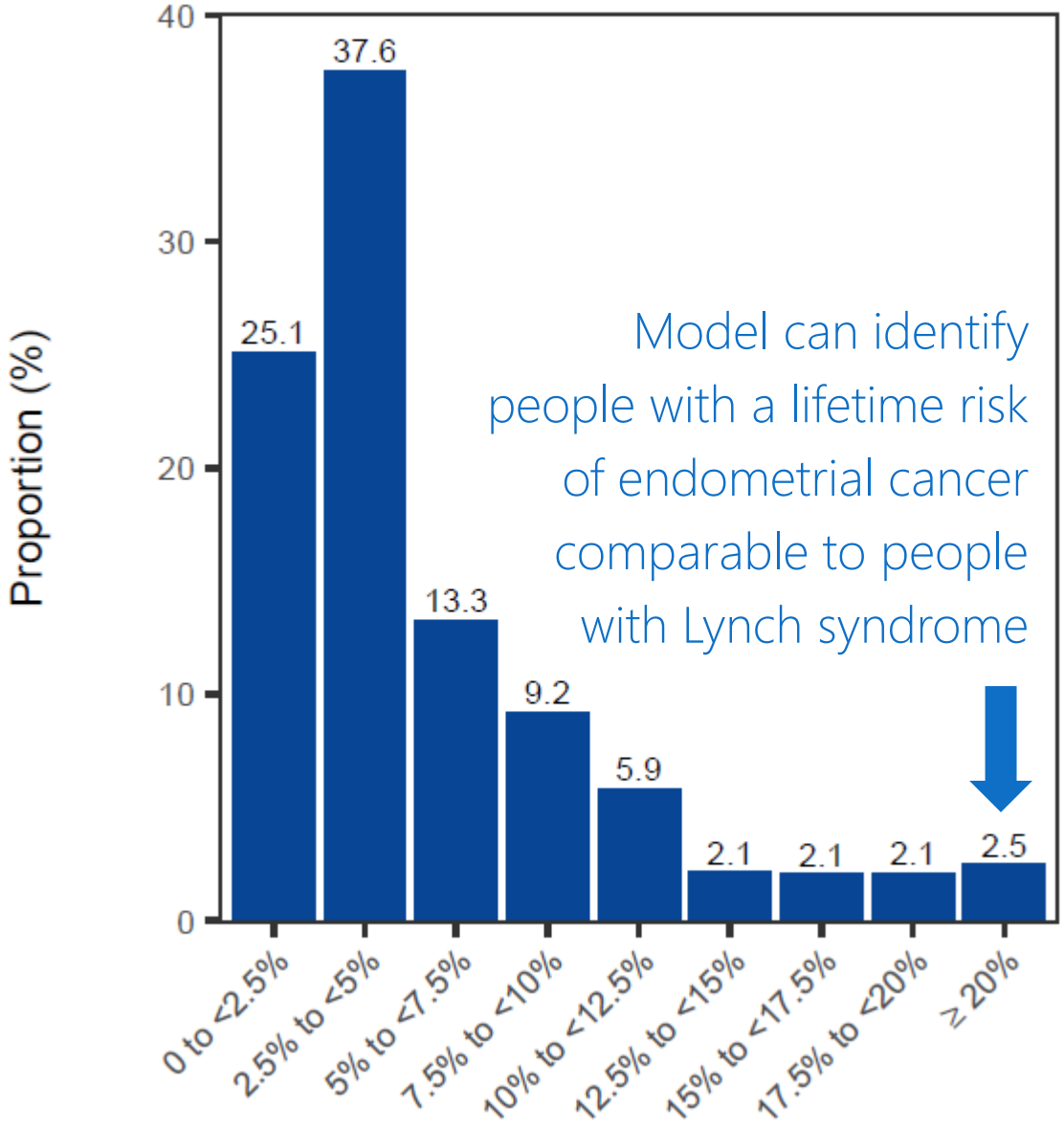


STRENGTHS.

SUMMARY

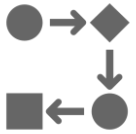
- Prediction model demonstrated moderate discrimination
- Well calibrated in NHS II and PLCO
- Based on clinical factors alone
- Minimal improvements with addition of published genetic factors

IMPLICATIONS

Potential tool for identifying people at high risk of endometrial cancer

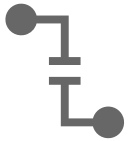
- Screening high risk individuals
- Risk-based prevention strategies
- Enrollment in prevention or screening trials

HOW DOES OUR MODEL COMPARE AGAINST PREVIOUS MODELS?



VARIABLE SELECTION

- Group LASSO vs. stepwise approaches
- Our models included more risk factors (e.g., education, E+P HT use, diabetes, hypertension)



DISCRIMINATION

- Smaller AUCs (0.64 to 0.69) in our model than EPIC (0.77)
- EPIC model largely driven by predictive contribution of age (AUC=0.71 in age-only model)

GENERALIZABILITY

- We used external data to estimate risk factor distributions and baseline incidence
- Previous models developed on selective populations

LIMITATIONS & NEXT STEPS.

AVAILABILITY OF RISK FACTORS

Could not include family history of endometrial cancer because these data were not collected in NHANES

RECALL BIAS

- Models based on case-control data
- Previous analyses of E2C2 data have reported similar RR estimates between cohort and case-control studies

AVAILABILITY OF GENETIC DATA IN NHS

- Genetic data pooled from GWAS of different disease outcomes
- Matching on factors may explain lower AUC

NEXT STEPS

Expanding to multi-racial/multi-ethnic populations

ACKNOWLEDGEMENTS.

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- Margaret Du

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- Bernard Rosner
- Miguel Hernan

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- UCB Fellowship

E2C2 collaborators and study participants

You can read more about the study here:

https://news.harvard.edu/gazette/story/2023/02/new-model-identifies-those-at-high-risk-for-endometrial-cancer/

https://pubmed.ncbi.nlm.nih.gov/36688725/

QUESTIONS?

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