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Projecting future benefits of cardiovascular risk factor control in today's young adults

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Outline

- **Role of CVD computer simulation in achieving one of NHLBI's *strategic goals*: <u>Advance Translational Research*</u>**

- **Young adults and short-term CVD risk**

- **Computer simulation of life long risk factor trajectories and cumulative exposure effects**

- **Projecting future benefits of controlling high cholesterol and blood pressure in young adults**

*https://www.nhlbi.nih.gov/about/documents/strategic-visioning/strategic-goals#3

Role of CVD computer simulation

- **"T3 &T4" Translation:** Computer simulation translates observational and trial evidence into information for decision-makers
- ***Scale up*** prevention interventions to the national population level

  Scale down national policies to states, counties, cities, health systems, clinics, worksites, employees/patients
- ***Extend* benefits and risks of interventions over time**: past the observation period of clinical trials, over the life course
- **Capture uncertainty** in current knowledge; identify crucial missing information and plan future intervention trials

The CVD Policy Model (1985-present)

- **Comparative value of primary and secondary prevention of coronary heart disease***
- ***Potential impact of population-wide prevention†***
  - *Dietary salt reduction (U.S., Argentina, and China)*
  - *Sugar-sweetened beverage tax (U.S., California, Mexico)*
  - *Smoke-free laws (U.S. and California)*
- ***Comparative effectiveness of clinic-based prevention in U.S. adults and in sub-populations‡***
  - *Hypertension guidelines (U.S., U.S. race/ethnic groups, China)*
  - *Lipid guidelines (U.S.)*
  - *PCSK9 inhibitors (U.S. patients with CVD, familial hypercholesterolemia)*

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*Goldman, *JACC*, 1999
†Bibbins-Domingo, *NEJM*, 2010; Wang *PLOS One* 2016
Wang, *Health Affairs*, 2012; Mekonnen, *PLOS One*, 2013;
Sanchez, under review; Lightwood, *Prev Med*, 2009
‡Moran, *NEJM*, 2015; Gu *PLOS Med* 2015; Lazar, *Circulation*, 2011; *ICER report* 2015 and under review

CVD risk factors in young adults (age18-39)

- The 10-year CVD risk paradigm often limits treatment to older patients; does not consider past risk factor exposure history
- Clinical guideline committees prioritize data from randomized clinical trials: average duration of trials is ≤ 5 years
- Increasingly, exposure histories recorded in EHRs
- Recently 5.7 million young adults took up health insurance (10% increase in this group) + increased interest in worksite prevention programs (AHA and corporations)

A patient in the primary care clinic…

<u>**40 year old male patient:**</u>

TC 215 mg/dl
HDL 45 mg/dl
LDL 140 mg/dl
Smoking: no
Diabetes: no
SBP 135 mm Hg
BP = untreated

10-yr ASCVD risk = 1.6%
Lifetime ASCVD risk = 46%

Treatment example

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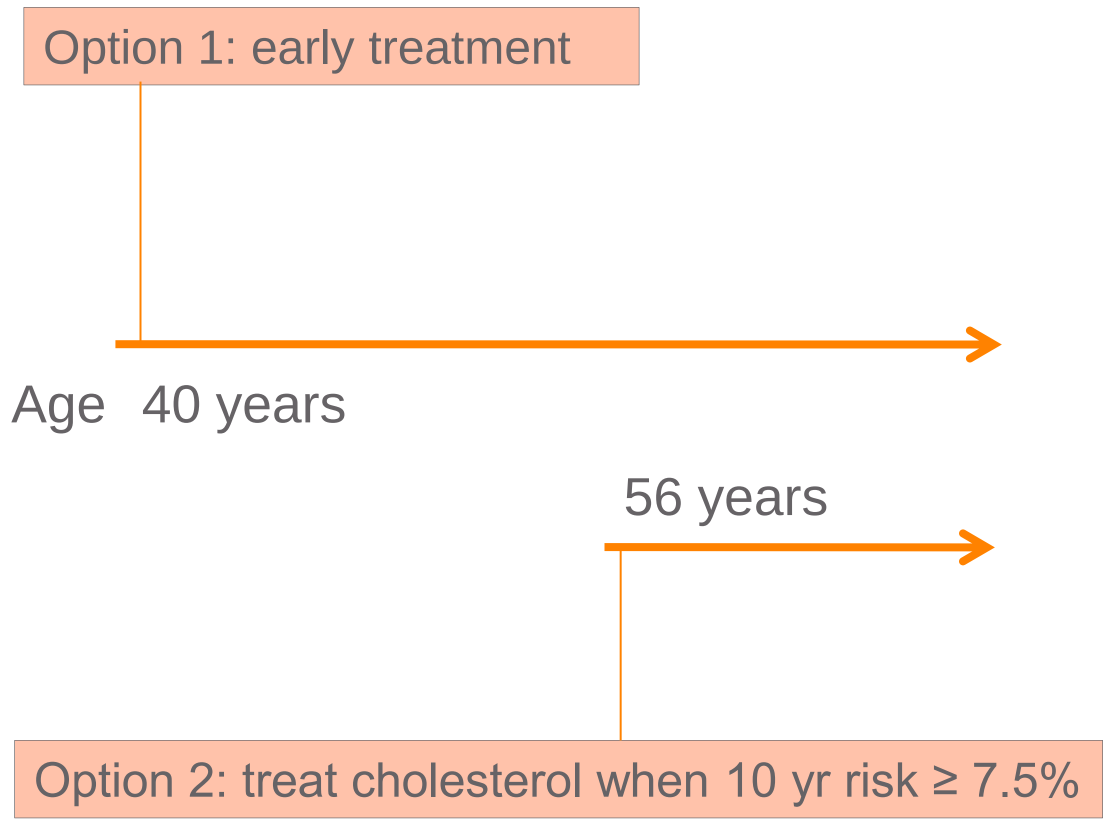

Treatment example

30 year old male patient:

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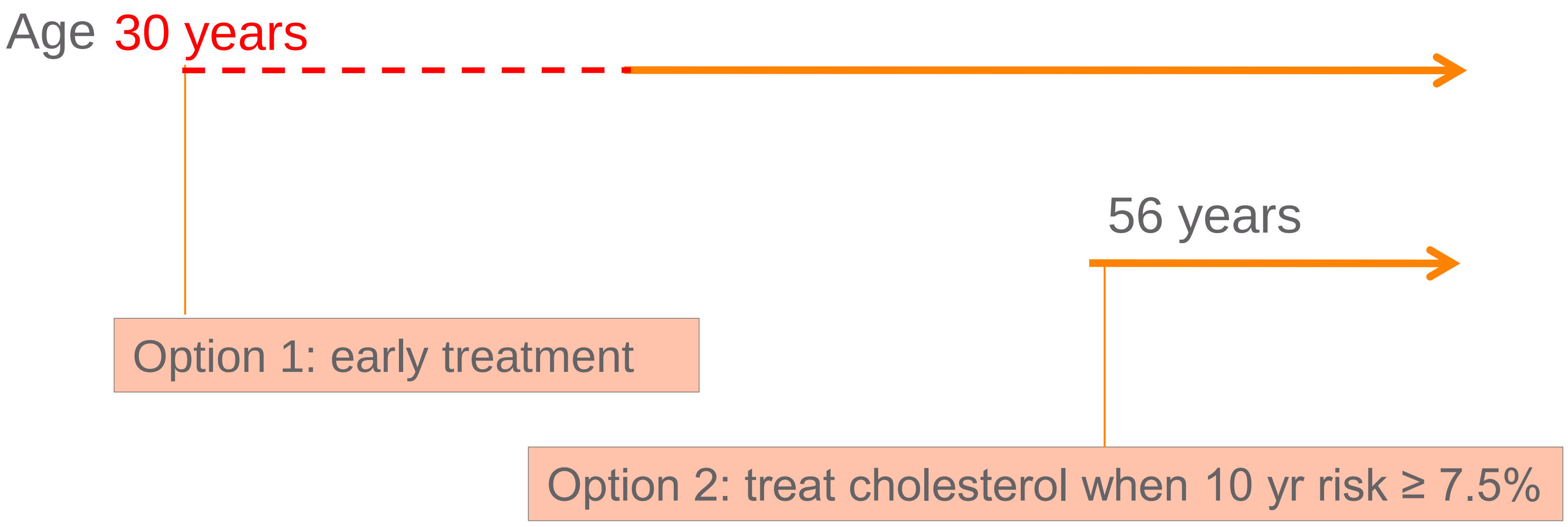

Effect of early exposures on later life CVD (all Framingham Heart Study data)

- Harris et al*: SBP ≥160 mmHg before age 65 had 1.8 x risk of CVD after 65 even after adjusting for later life SBP
- Navar-Boggan et al**: years of exposure to non-high-density lipoprotein cholesterol ≥ 160 mg/dL before age 55 was an independent predictor of later life CVD risk
- We set out to estimate the independent effects of young adult (age 20-39) time-weighted average risk factor exposures on later life CVD risk***

*Harris et al., Hypertension, 1985

**Navar-Boggen et al., Circulation, 2015

***Pletcher et al., under review

Life course risk factor trajectories from age 20-90 years: the Framingham Offspring Study

- Data from 4,860 ppts
- Mixed effects model; best linear unbiased predictions
- Restricted cubic splines with three knots (ages)
- Included onset or withdrawal of lipid-lowering and antiHT medications

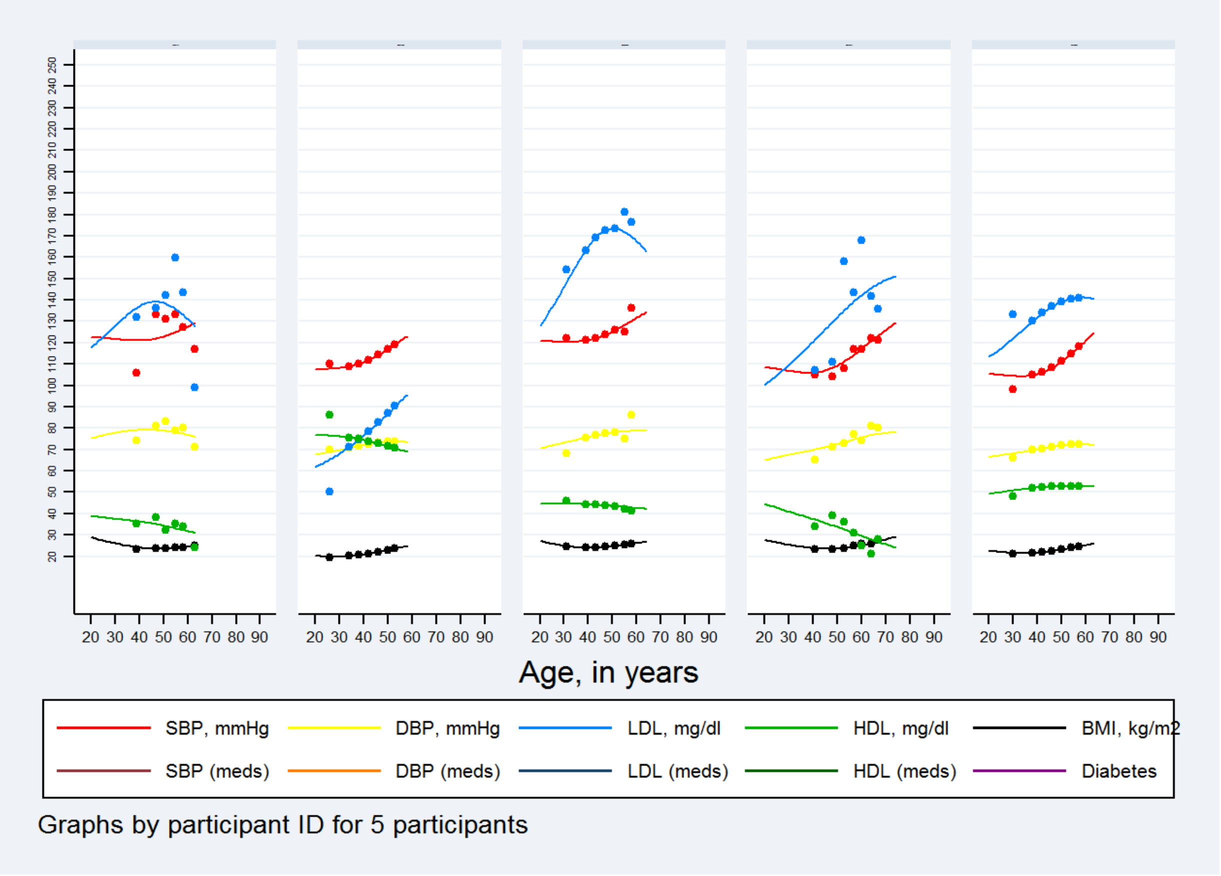

Figure. Risk factor trajectories in Framingham Offspring Cohort individuals not taking medications

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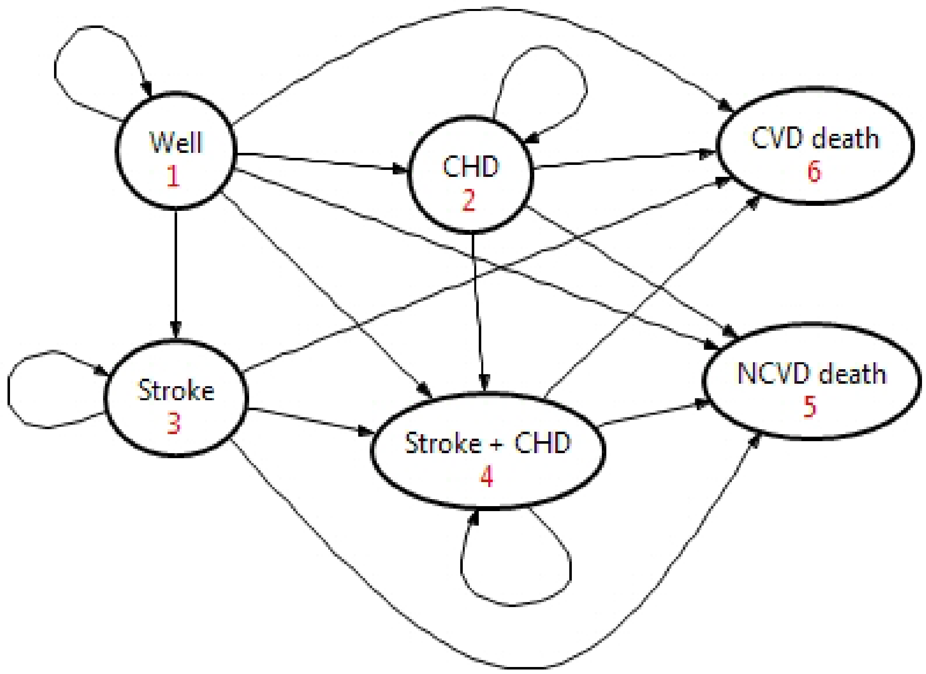
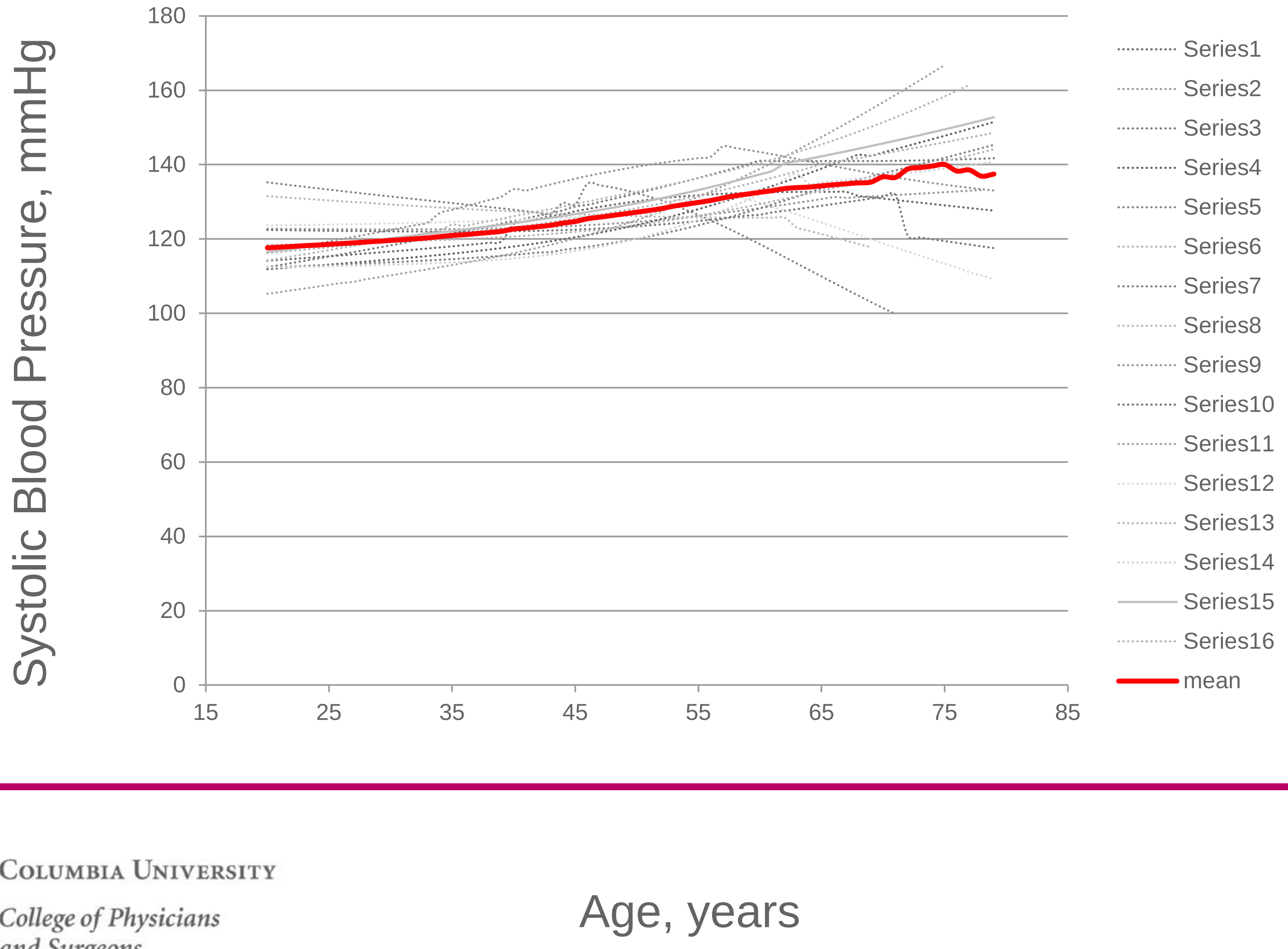
Microsimulation version of the CVD Policy Model

- CVD Microsimulation Model (TreeAge 2016)
- Probability sampling of NHANES participants
- Structure, many inputs from the CVD Policy Model
- Validated by parallel simulations with CVD Policy Model, national life tables
- 10-yr CVD risk calculated annually using ASCVD (AHA/ACC) calculator



Structure of the CVD Microsimulation Model (CVDMM)

"Lifetime" risk factor trajectories



Framingham Offspring Results

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DATA ARE FROM MANUSCRIPT UNDER JOURNAL REVIEW

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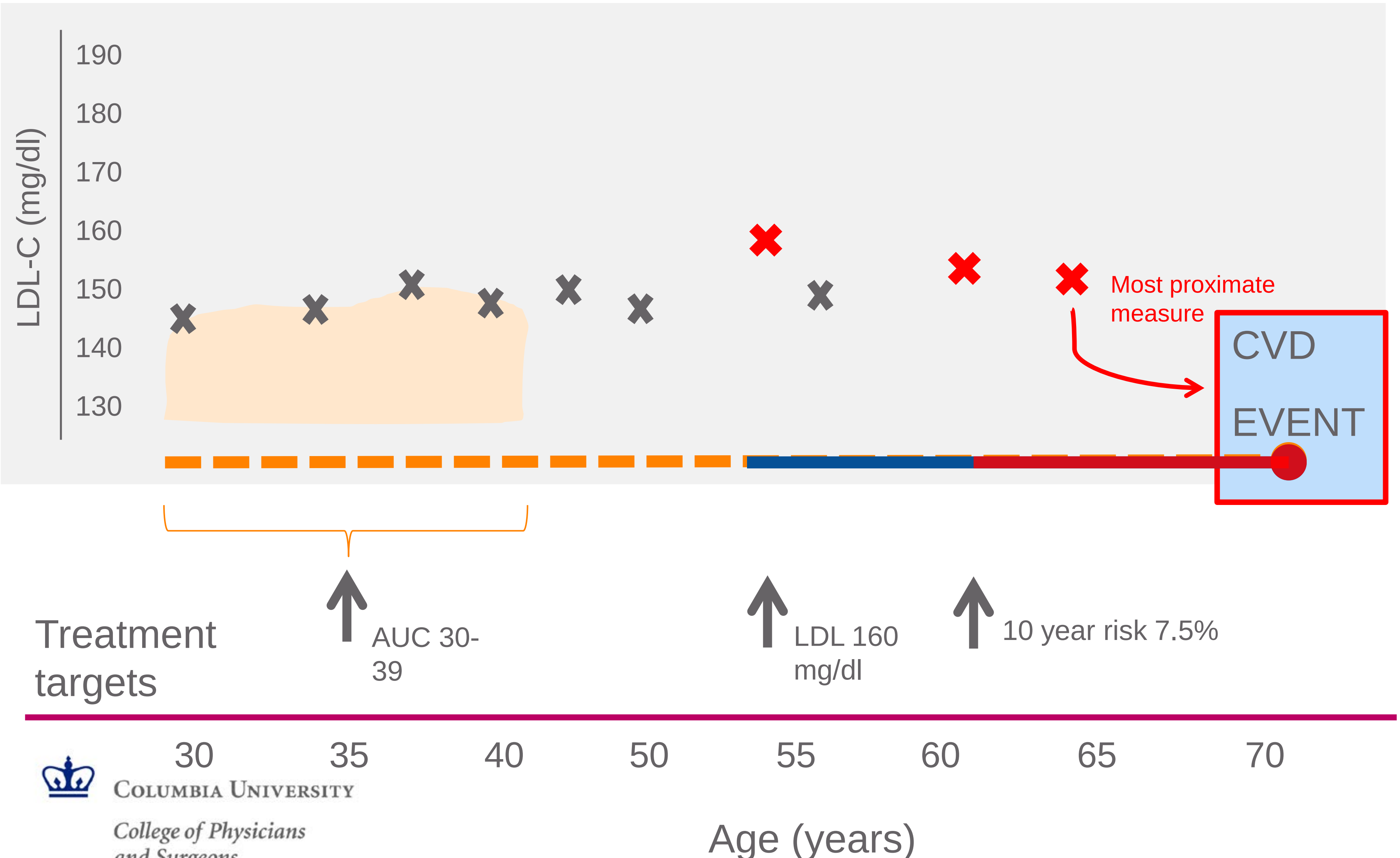
Hazard ratios (**Y-axis**, with 95% confidence intervals) are adjusted for age (via Cox model), sex, calendar year (via spline), body mass index, diabetes, years with diabetes, smoking status (current/past/never), pack-years of tobacco exposure (via spline), and use of blood pressure and lipid medications.

X-axis: categories for systolic blood pressure (SBP) are <=120 (reference), 121-140, 141-160 and >160 mmHg; for diastolic blood pressure (DBP) are <=80, 81-90, 91-100, and >100; for low-density lipoprotein cholesterol (LDL) are <=100 (reference), 101-130, 131-160 and >160 mg/dl; and for high-density lipoprotein cholesterol (HDL) are >65 (reference), 51-65, 36-50, and <=35 mg/dl. "P Overall" refers to a test of the overall contribution of the risk factor (including early, later, and current exposures) to the model. No participants had an average SBP>160 mmHg from age 20-39. The * indicates a truncated confidence interval.

Hypothetical adult life course risk factor exposures and event prediction



Adult life course risk factor exposures and CVD event prediction

Model event prediction, adding young adult exposure effects.

- Annual probabilities of first CVD events or non-CVD deaths are determined by functions in the form of competing risk, Cox proportional hazard regression equations.
- The equation below adds time-weighted average young adult risk factor exposure to the standard risk function that incorporates only “current” risk factor information:

$$\frac{e^{\left(\alpha + \beta_{age} \times AGE + \sum \beta_{RF} \times MEAN_{RF} + \sum \beta_{TWA} \times TWA\right)}}{1 + e^{\left(\alpha + \beta_{age} \times AGE + \sum \beta_{RF} \times MEAN_{RF} + \sum \beta_{TWA} \times TWA\right)}}$$

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where α = rate of disease in the overall population (intercept), β = risk factor beta coefficient, and RF = current risk factor, MEAN = risk factor “current” mean exposure level (exposure most proximate in time prior to first event), TWA = time-weighted average risk factor exposure, ages 20-39 years

R01 HL107475-01 (Renewal)

Aim 1. Estimate the potential impact and cost-effectiveness of CVD risk factor control during young adulthood, accounting for potential cumulative atherosclerotic damage from early life exposure

We hypothesize that 1) control of elevated diastolic BP (<90 mmHg) and LDL-C (<130 mg/dl) before age 40 years would yield superior lifetime gains in quality-adjusted life years compared with controlling BP and cholesterol according to 10-year risk after age 40 years, and that millions of young adults could potentially benefit from early adult risk factor control, but that 2) these benefits will be very sensitive to adverse event rates and any potential quality of life decrement associated with taking preventive medications on a daily basis.

Aim 2. Project impact, as above, through 2050 accounting for the ongoing obesity epidemic in young adults

Approach to NHLBI observational cohorts data

Current analyses in Framingham Offspring study data (BioLINCC data)

Other cohorts we plan to study:

Younger ages: Bogalusa Heart Study, CARDIA

Older ages: MESA, ARIC, REGARDS, CHS

By pooling cohorts, extend the age range, move closer to “life course” perspective, and add racial/ethnic/socio-economic/geographic diversity

Pooling individual participant data from cohorts will increase number of events and be more robust in terms of co-morbidities

We all cut our teeth working with NHLBI cohort data and we are excited about the prospect of working with the CCC and generating more value from the public’s investment in NIH research.

Thank you!

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- Michelle Odden

Extra Slides

Effect sizes for prevention interventions

Relative risk of CVD	Main	Lower	Upper	Reference
Short-term effects: later life adult risk factor reductions in clinical trials				
-5 mmHg DBP, -10 mm Hg SBP				
CHD	**0.73**	**0.70**	**0.77**	Law, Morris and Wald meta-analysis, BMJ, 2009
Stroke	**0.64**	**0.59**	**0.69**	
-30 mg/dl LDL-C*				
CHD	**0.76**	**0.73**	**0.79**	Cholesterol Treatment Trialists, Lancet 2008
Long-term effects: time weighted average exposure, ages 20-39 years				
-5 mmHg time-weighted average DBP				
CHD	**0.79**	**0.66**	**0.95**	Pletcher et al. analysis of the Framingham Offspring Study, preliminary data, under review
Stroke	**To be added**	**To be added**	**To be added**	
-30 mg/dl time-weighted average LDL-C				
CHD	**0.67**	**0.50**	**0.91**	

Effect sizes for prevention interventions

Change with intervention (follow up time)	Diastolic BP reduction, mmHg	LDL-C reduction, mg/dl	FPG reduction, mg/dl
Diet & lifestyle change* **USPSTF Meta-analysis (12-24 m)** **PREMIER exercise+DASH (6 m)*** **DPP lifestyle change arm (36 m)**	 1.0 (95%CI,0.7-1.9) 3.2 (95%CI,2.0-4.3) 3.8 (SE, 0.3)	 **4.2** (95%CI,0.7-7.8) **5.1** (95%CI,9.9-0.3) **4.5** increase (SE, 4.8)	 **1.9** (95%CI,0.5-3.2) **4.0** (SE, 1.6)
Pharmacotherapy † **(various; most trials conducted over <5 years or 60 m)**	Meds from 1 of 4 standard classes. For each standard dose: 5.1+0.11 × (pDBP-97)	HMG-CoA reductase inhibitor (statin) **10-80%** reduction, depending on agent and dose	Metformin 850 mg twice daily **4.0** (SE, 1.6)

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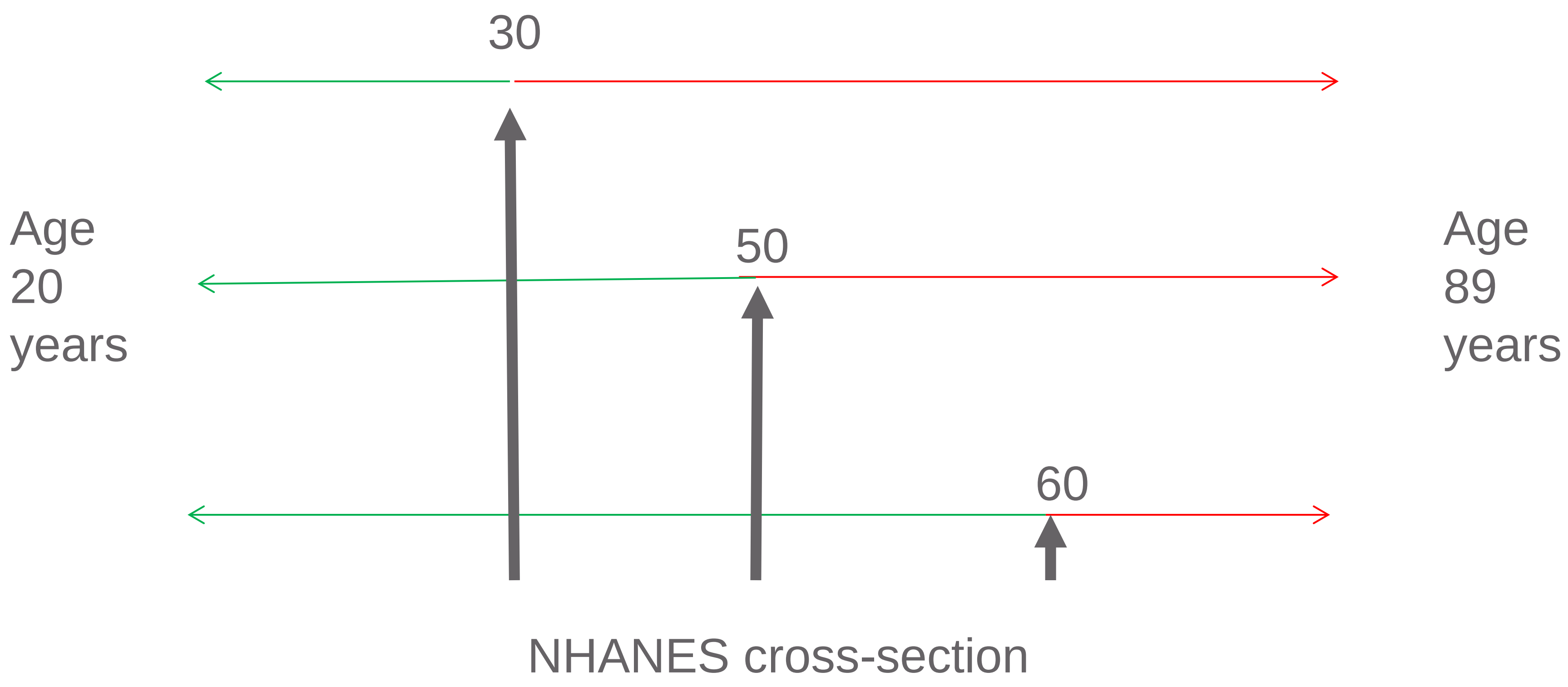
*USPSTF, PREMIER, DPP

†Law, Morris Wald; Cholesterol trialists; DPP

Back and forward imputation of risk factor “histories” for NHANES participants using Framingham



Results: Table 1; CVDMM* vs. CVDPM†

Cumulative events per 1,000 person-years, 30-year simulation	Males		Females	
	CVDPM	CVDM	CVDPM	CVDM
New stroke case	53.3	56.0 (51.5-60.5)	42.2	41.4 (37.5- 45.3)
New CHD case	199.6	198.3 (190.5- 206.1)	112.2	112.6 (106.4- 118.8)
Stroke death	8.2	7.2 (5.5- 8.9)	6.3	5.1 (3.7- 6.5)
CHD death	26.9	26.7 (23.5-29.9)	12.1	10.8 (8.8- 12.8)
NCVD death	191.1	192.6 (184.9- 200.3)	136.8	137.4 (130.6- 144.2)
Total death	226.3	226.5 (218.3- 234.7)	155.2	153.3 (146.2- 160.4)

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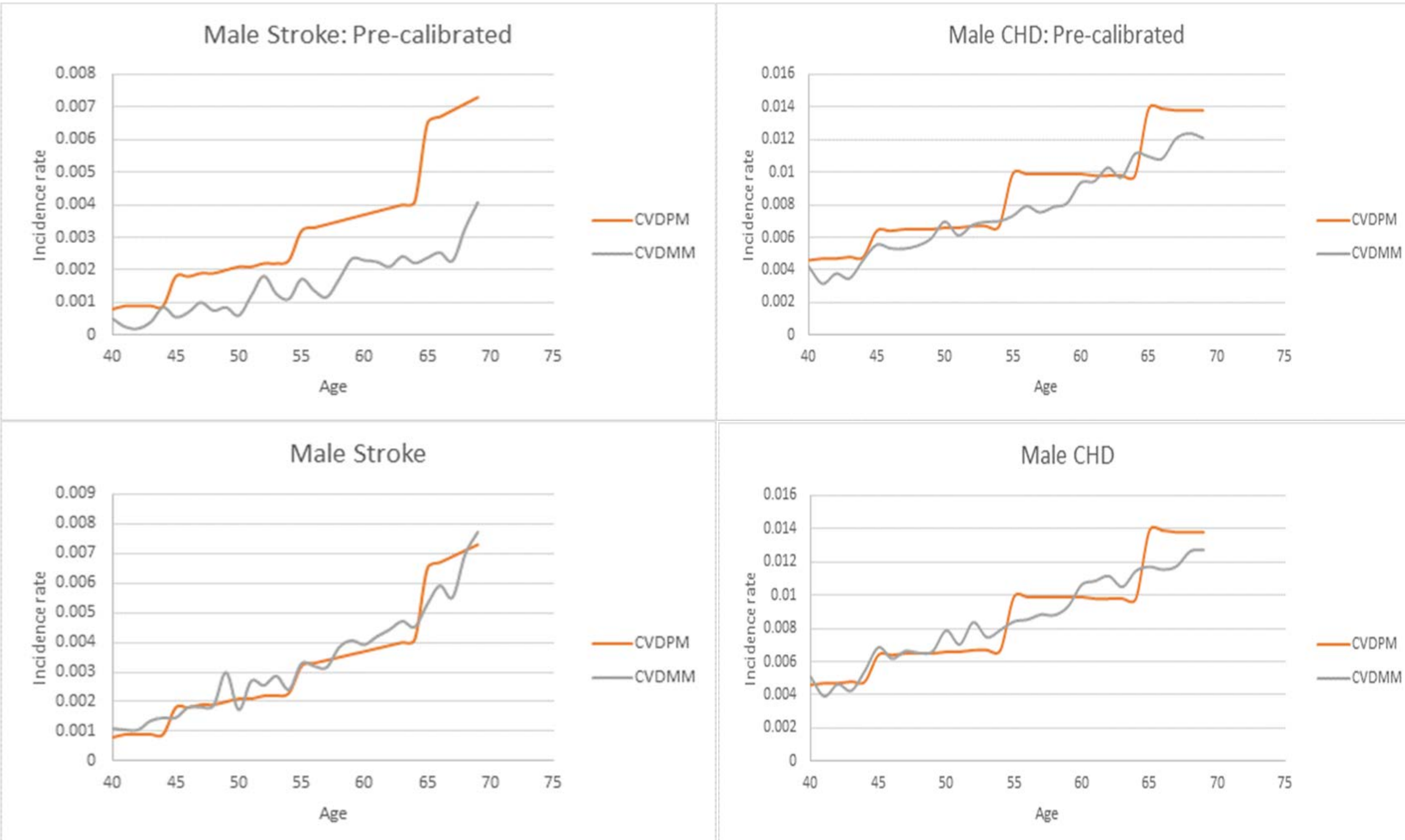
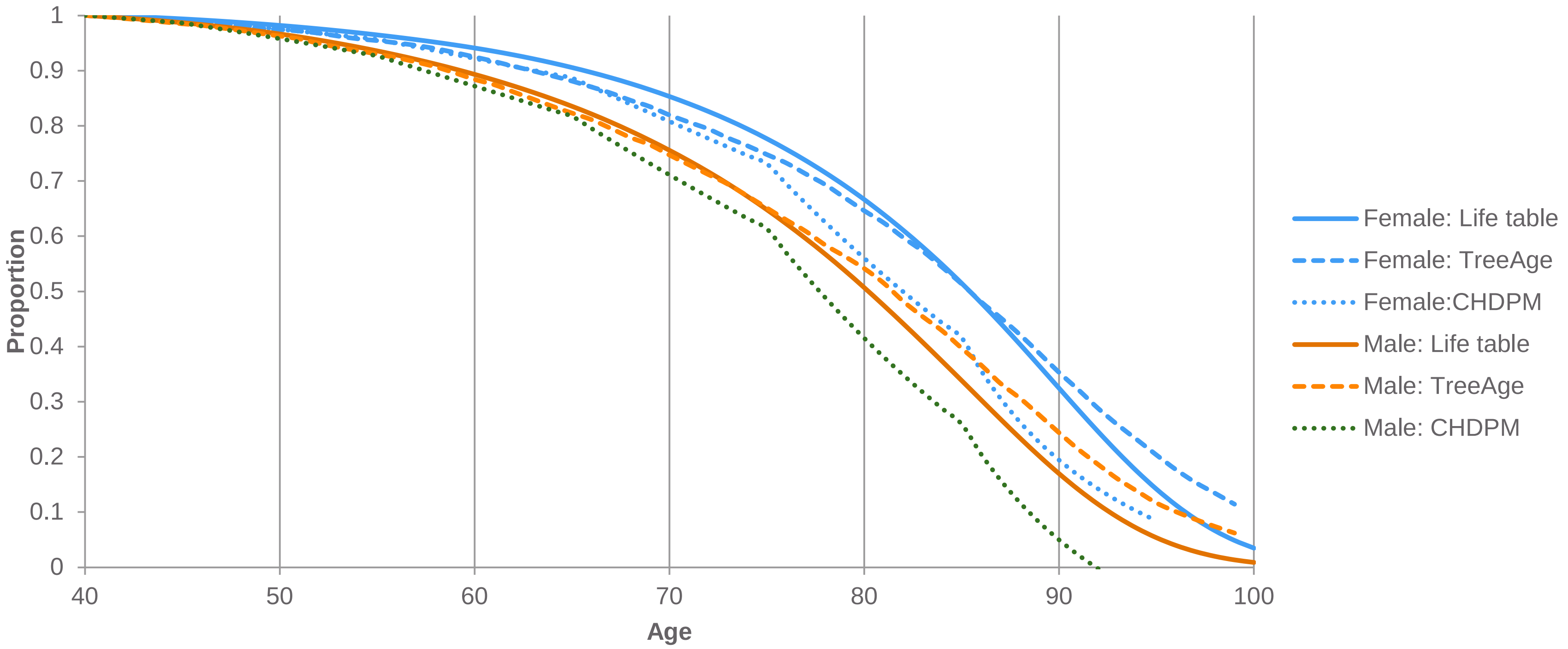
*CVDMM = CVD microsim model (TreeAge)

†CVDPM = CVD Policy Model (Fortran)

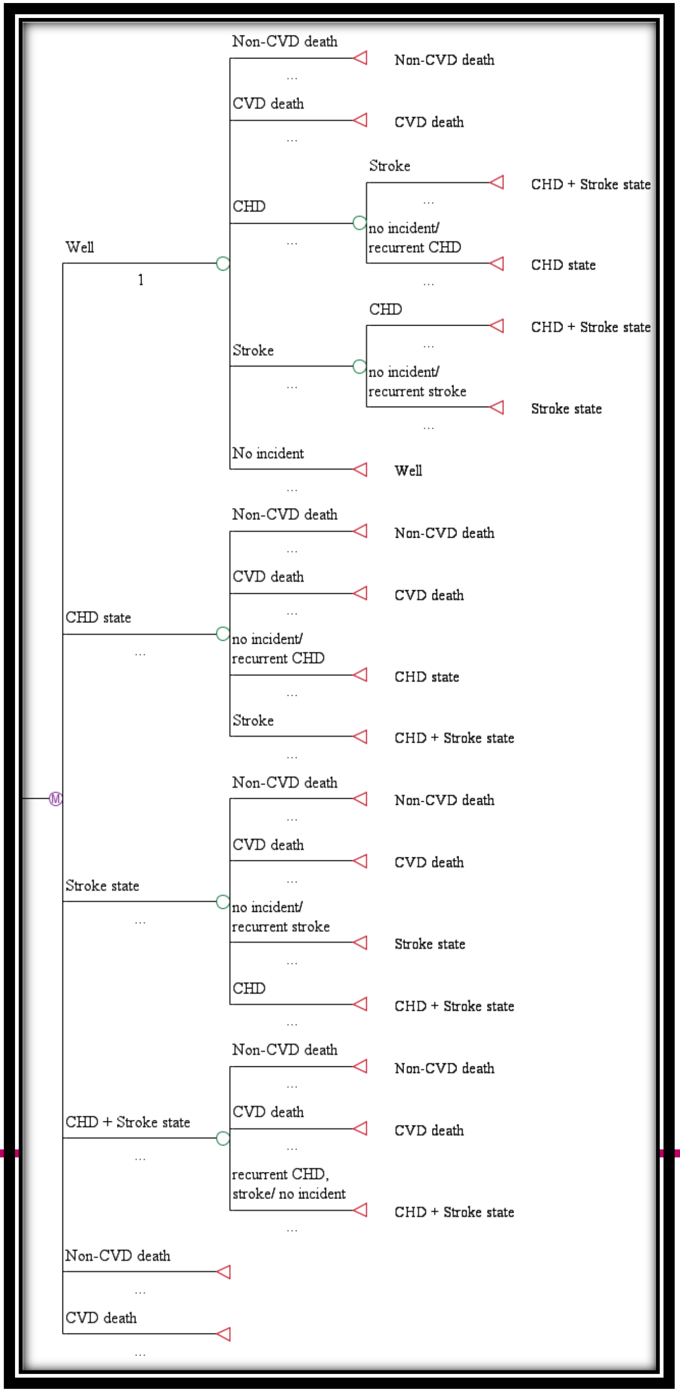
CVD Microsimulation Model Calibration



Survival curve from life table, CVDPM and CVD microsimulation model



National CVD microsimulation model: structure



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