

SUPPLEMENTAL MATERIAL

Quantifying importance of major risk factors for coronary heart disease

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Supplemental Methods

Imputation of on-treatment values

The algorithm for imputation of on-treatment SBP can be summarized with the following steps (as described in Tobin MD, Sheehan NA, Scurrah KJ, Burton PR. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. *Stat Med.* 2005;24:2911–2935):

- a. Compute the mean SBP value in the sample and subtract from each individual observation to obtain estimated raw residuals (r_i)
- b. Sort raw residuals in descending order and apply the following computation to each in turn (in descending order) to derive an adjusted residual r_k^* :

$$r_k^* = r_k(1 - \text{treat}_k) + \text{treat}_k \left(\left(r_k + \sum_{j=1}^{j=k-1} r_j^* \right) / k \right)$$

where for notational convenience, r_k now refers to the k th residual sorted in descending order and treat_k takes the value 1 if the k th ordered residual relates to a treated subject and 0 otherwise. The raw residual in a treated subject is therefore adjusted by taking an average of its original value and all larger (adjusted) residuals. Values relating to untreated individuals are left unchanged.

- c. Once all raw residuals have been converted to adjusted residuals they are sorted back into their original order, and adjusted SBP is defined as the observed SBP minus the raw residual plus the adjusted residual.

A similar algorithm was used to impute total cholesterol.

Calculation of expected ARR due to treatment

For lipids, every 38.7 mg/dL reduction in LDL-C is expected to reduce CHD risk by 25%. We assumed that each individual with LDL-C > 70 mg/dL would have their LDL-C reduced by 30% (consistent with moderate intensity statin). The resulting reduction in mg/dL was then translated into the expected relative reduction in risk, calculated as 0.75 to the power of observed reduction in mg/dL divided by 38.7 mg/dL (e.g., a reduction of 2×38.7 mg/dL results in relative risk reduction of 0.75×0.75). ARRs were estimated by multiplying the 10-year baseline risks by the above relative risk reduction, and the NNTs were computed as the inverse of the ARR.

For SBP, every 10-mmHg reduction is expected to lower risk by 21% (Karmali KN, Lloyd-Jones DM, Berendsen MA, Goff DC Jr, Sanghavi DM, Brown NC, Korenovska L, Huffman MD. Drugs for primary prevention of atherosclerotic cardiovascular disease: an overview of systematic reviews. *JAMA Cardiol.* 2016;1:341-349). We assumed that SBP of each individual can be lowered to 130 mmHg. Thus, we calculated the degree of elevation over 130 mmHg and divided it by 10 mmHg to obtain the exponent to which 0.79 needs to be raised (e.g., a person with SBP=150 mmHg, would have an expected reduction in SBP of 20 mmHg, leading to a relative risk reduction of $0.79^{*0.79}$). ARRs were estimated by multiplying the 10-year baseline risks by the above relative risk reduction, and the NNTs were computed as the inverse of the ARR.

Supplemental Table 1. Summary of patient selection

	ARIC	CHS	Offspring	MESA	Overall
Visit/exam	3	3	6	1	
Available at visit/exam	12118	4504	3434	6814	26870
Age exclusion	(0)	(315)	(236)	(7)	(558)
History of CVD	(1707)	(1228)	(410)	(9)	(3354)
Missing covariates/no follow-up	(238)	(3)	(5)	(86)	(332)
Analyzed	10173	2958	2783	6712	22626

ARIC = Atherosclerosis Risk in Communities; CVD = cardiovascular disease; CHS = Cardiovascular Health Study; MESA = Multi-Ethnic Study of Atherosclerosis.

Supplemental Table 2. Effect of study on hazard ratios

	STUDY not in the model	STUDY as fixed effect	STUDY as Strata	STUDY as Random Effect
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Sex (male)	1.834 (1.681–2.000)	1.930 (1.769–2.106)	1.930 (1.769–2.106)	1.928 (1.767–2.104)
Race (AA)	0.929 (0.827–1.044)	1.045 (0.925–1.180)	1.042 (0.923–1.177)	1.043 (0.924–1.178)
Age	1.779 (1.695–1.867)	1.525 (1.435–1.620)	1.521 (1.432–1.616)	1.531 (1.441–1.626)
Non-HDL-C	1.186 (1.141–1.233)	1.179 (1.135–1.226)	1.179 (1.134–1.226)	1.179 (1.135–1.226)
SBP	1.332 (1.276–1.391)	1.346 (1.288–1.405)	1.346 (1.289–1.406)	1.345 (1.288–1.405)
Smoking	2.065 (1.853–2.301)	1.999 (1.794–2.228)	2.000 (1.795–2.229)	2.000 (1.795–2.229)
Diabetes	1.840 (1.659–2.041)	1.885 (1.698–2.091)	1.885 (1.699–2.091)	1.884 (1.698–2.090)

AA = African American; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure.

Hazard ratios for age, SBP and non-HDL-C represent 1 SD increase. Age SD = 8.9, SBP SD = 27.8, non-HDL-C SD = 39.9.

Supplemental Table 3. Hazard ratio, population attributable fraction, and absolute risk reduction with treatment for 10-year risk of CHD adjusting for competing risk of non-cardiovascular mortality

Risk Factor	Hazard Ratio (95% CI)		Population Attributable Fraction (95% CI)		Total Average Risk	ARR With Treatment
	Only RF*	Fully Adjusted	% \geq 130	PAF \geq 130		
Treatment-adjusted SBP†	1.55 (1.49-1.60)	1.33 (1.27-1.39)	53.7	27.6 (22.6-32.2)	10.0	2.6
Treatment-adjusted non-HDL-C‡	1.20 (1.15-1.25)	1.20 (1.15-1.24)	74.4	18.5 (11.8-24.7)	10.0	2.4
Smoking	1.50 (1.35-1.67)	1.97 (1.77-2.19)	14.8	9.1 (7.3-10.8)		
Diabetes	2.25 (2.04-2.49)	1.81 (1.63-2.01)	12.4	9.2 (7.3-11.0)		

ARR = absolute risk reduction; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; PAF = population attributable fraction; RF = risk factor; SBP = systolic blood pressure.

*Only RF refers to model with a single risk factor; Fully Adjusted refers to a model with all risk factors (sex, race, age, non-HDL-C ratio, adjusted SBP, smoking, diabetes); Total Average Risk is the mean of all estimated risks; ARR With Treatment describes the absolute amount of total risk that can be eliminated with treatment.

†Hazard ratio for 1 SD increase in SBP (SD = 27.8). ‡Hazard ratio for 1 SD increase in non-HDL-C (SD = 39.91).

Supplemental Table 4. Hazard ratio, population attributable fraction, and absolute risk reduction with treatment for 10-year risk of CHD by sex

Risk Factor		Hazard Ratio (95% CI)		Population Attributable Fraction (95% CI)		Total Average Risk	ARR With Treatment
		Only RF*	Fully Adjusted	% ≥ 130	PAF ≥ 130		
Treatment-adjusted SBP†	Male	1.51 (1.43-1.59)	1.28 (1.21-1.36)	53.5	22.7 (16.3-28.6)	13.9	4.5
	Female	1.68 (1.58-1.78)	1.39 (1.31-1.49)	53.9	35.9 (28.1-42.8)	8.2	3.2
Treatment-adjusted non-HDL-C‡	Male	1.13 (1.07-1.19)	1.18 (1.12-1.24)	75.4	18.8 (10.2-26.6)	13.9	3.4
	Female	1.28 (1.21-1.36)	1.19 (1.12-1.26)	73.7	12.4 (0.9-22.5)	8.2	2.1
Smoking	Male	1.46 (1.27-1.68)	1.92 (1.66-2.21)	15.7	9.1 (6.7-11.3)		
	Female	1.57 (1.34-1.85)	2.32 (1.96-2.74)	14.2	10.9 (8.2-13.4)		
Diabetes	Male	2.00 (1.75-2.29)	1.67 (1.45-1.91)	13.9	8.3 (5.8-10.7)		
	Female	2.61 (2.24-3.05)	2.15 (1.83-2.52)	11.2	11.6 (8.8-14.4)		

ARR = absolute risk reduction; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; PAF = population attributable fraction; RF = risk factor; SBP = systolic blood pressure.

*Only RF refers to model with a single risk factor; Fully Adjusted refers to a model with all other risk factors (race, age, non-HDL-C ratio, adjusted SBP, smoking, diabetes); Total Average Risk is the mean of all estimated risks; ARR With Treatment describes the absolute amount of total risk that can be eliminated with treatment.

†Hazard ratio for 1 SD increase in SBP (SD = 27.8). ‡Hazard ratio for 1 SD increase in non-HDL-C (SD = 39.91).