

Metabolic mediators of sex/gender: Do risk factors explain the gender gap in coronary heart disease?



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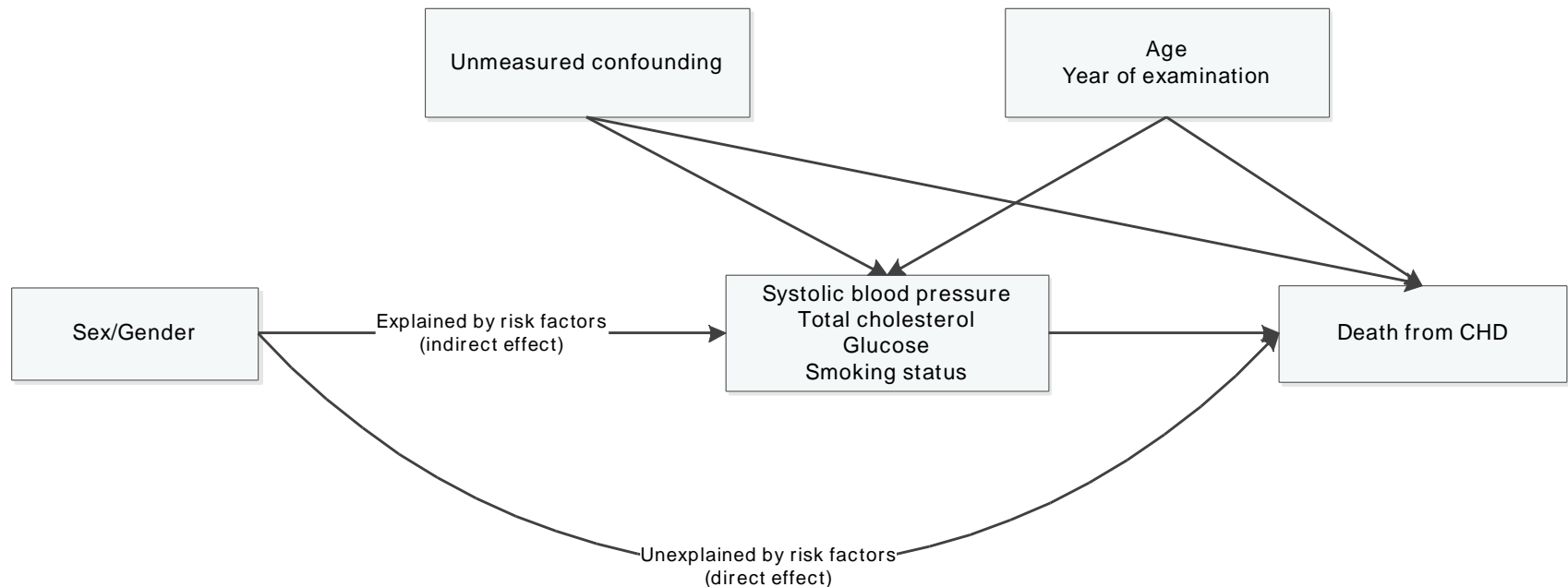
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Situation



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- Sex/Gender influences CHD risk factors which in turn affect the outcome (death from CHD).
- Estimate effects of the different paths.

CHD as death cause

Table 1 Number and percentage of deaths from cardiovascular diseases in Europe—latest available year^a

	Cardiovascular disease (total)		Coronary heart disease		Cerebrovascular disease		Other cardiovascular diseases	
Males								
Total deaths (all ages)	1 862 774	42%	876 017	20%	429 756	10%	557 001	12%
Premature deaths—before age 75	939 698	36%	473 501	18%	201 780	8%	264 417	10%
Premature deaths—before age 65	508 132	31%	253 432	16%	95 249	6%	159 451	10%
Females								
Total deaths (all ages)	2 219 326	51%	903 330	21%	627 227	14%	688 769	16%
Premature deaths—before age 75	536 712	37%	232 683	16%	155 702	11%	148 327	10%
Premature deaths—before age 65	201 492	27%	77 166	10%	54 470	7%	69 856	9%
Total								
Total deaths (all ages)	4 082 100	46%	1 779 347	20%	1 056 983	12%	1 245 770	14%
Premature deaths—before age 75	1 476 410	37%	706 184	18%	357 482	9%	412 744	10%
Premature deaths—before age 65	709 624	30%	330 598	14%	149 719	6%	229 307	10%

^aNo data available for Andorra. Source: World Health Organization Mortality Database.

Source: Nichols et al. Cardiovascular disease in Europe 2014: epidemiological update.
European Heart Journal (2014)

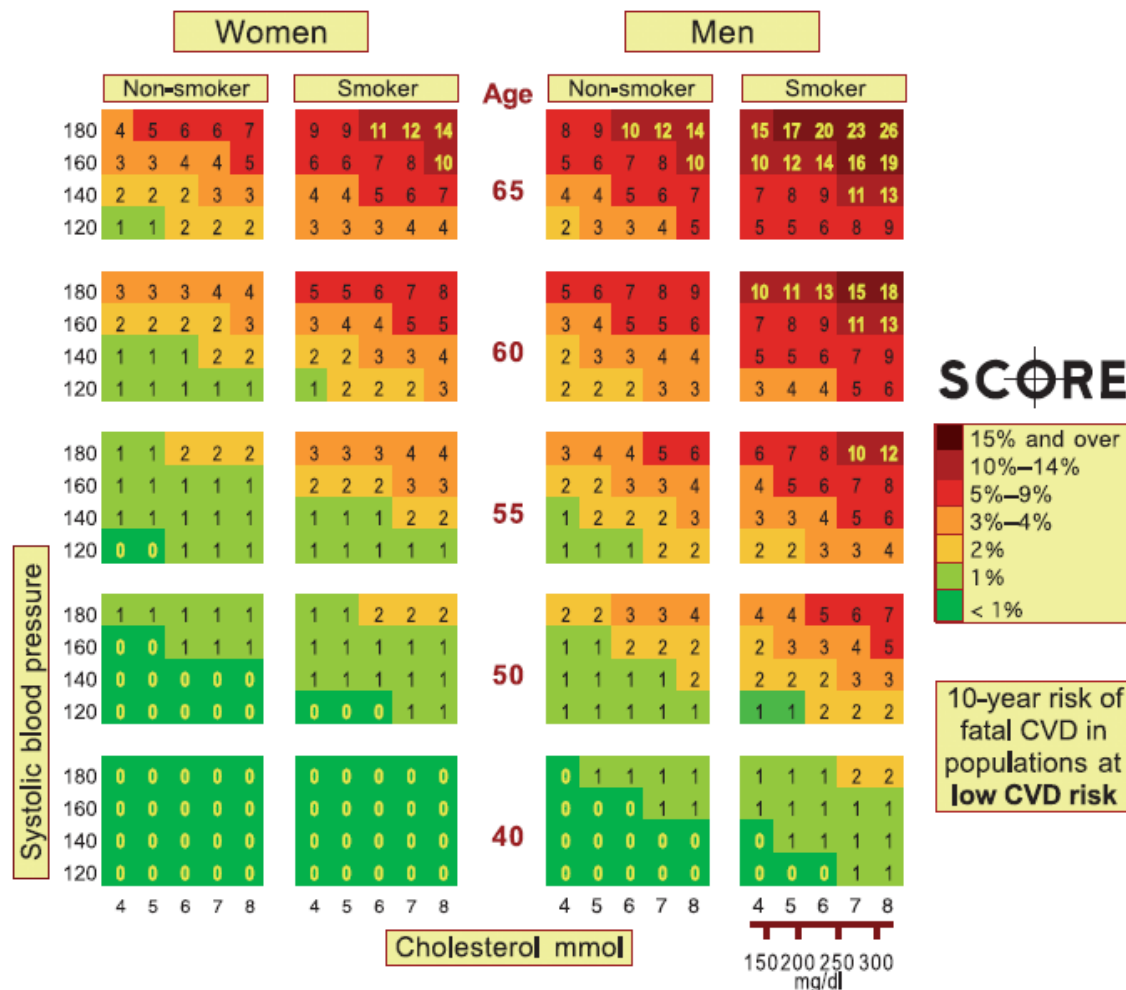
CHD and risk factors (1)



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- Fixed
 - Age
 - Sex
 - Genetics
 - ...
 - Modifiable
 - Blood pressure
 - Type 2 diabetes
 - Smoking
 - Lipids (cholesterol, triglycerides)
 - Body weight
 - ...
-
- Prevention is possible via control of modifiable risk factors.

CHD and risk factors (2)



Ten-year risk of fatal cardiovascular disease in populations at low cardiovascular disease risk.

Source: Conroy et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. European Heart Journal (2003)

Sex and age differences in major CHD risk factors



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TABLE 2. MEANS AND SD OF RISK FACTOR VALUES BY SEX AND AGE GROUP AT FIRST EXAMINATION, VHM&PP, 1985–1999

	Men				Women			
	20–34 years	35–49 years	50–64 years	≥65 years	20–34 years	35–49 years	50–64 years	≥65 years
Body mass index (kg/m ²) ^a	24.1 (3.3) ^b	25.8 (3.5)	26.4 (3.5)	25.8 (3.5)	22.3 (3.8)	24.7 (4.5)	26.5 (4.6)	26.1 (4.4)
Systolic blood pressure (mm Hg)	125.8 (14.8)	130.6 (17.1)	140.5 (20.0)	148.6 (21.1)	116.9 (14.0)	126.1 (18.4)	141.3 (21.2)	153.1 (21.6)
Diastolic blood pressure (mm Hg)	78.6 (9.8)	82.7 (10.9)	85.3 (11.2)	84.4 (10.6)	74.8 (9.4)	79.8 (10.8)	85.1 (11.2)	85.4 (10.9)
Total cholesterol (mg/dl)	199.3 (42.6)	228.6 (45.8)	237.0 (45.8)	232.5 (45.5)	193.4 (36.1)	212.4 (40.4)	246.2 (45.6)	250.9 (47.3)
Total cholesterol (mmol/L)	5.2 (1.1)	5.9 (1.2)	6.1 (1.2)	6.0 (1.2)	5.0 (0.9)	5.5 (1.0)	6.4 (1.2)	6.5 (1.2)
Triglycerides (mg/dl)	131.7 (91.9)	171.2 (120.1)	168.6 (112.6)	151.0 (94.1)	97.7 (51.0)	107.9 (65.8)	135.1 (79.9)	150.9 (85.6)
Glucose (mg/dl)	82.3 (15.6)	89.1 (23.9)	95.5 (32.2)	98.5 (35.7)	80.7 (13.8)	86.8 (19.8)	92.9 (27.7)	98.6 (34.0)
Gamma gt (mg/dl)	18.3 (22.1)	28.5 (40.4)	30.1 (40.9)	26.0 (34.8)	10.3 (11.4)	14.0 (22.1)	17.7 (22.7)	18.5 (22.7)
Regular smoking	30.3%	28.3%	23.1%	14.7%	26.3%	19.8%	9.7%	4.2%

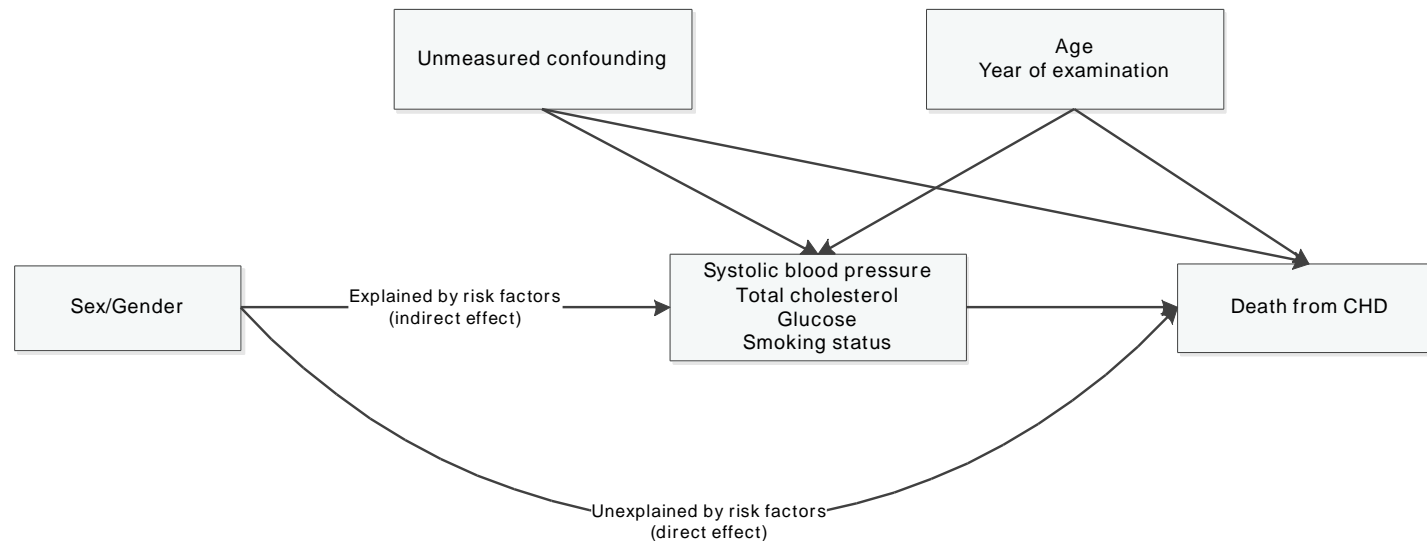
^aExcluding 2,100 (1.4%) missing values within body mass index and blood pressure and 4,500 (3.1%) missing values within cholesterol, triglyceride, glucose, and gamma-gt (values missing partly due to missing consent of the participants)

^bMeans (SD).

Source: Ulmer et al. Why Eve is not Adam: prospective follow-up in 149650 women and men of cholesterol and other risk factors related to cardiovascular and all-cause mortality. Journal of Women's Health (2004)

Research question (1)

- In general, men have a higher CHD mortality risk than women, especially at younger ages.
- Men have also other risk factor profiles (TC, blood pressure, glucose, smoking) than women.



Research question (2)

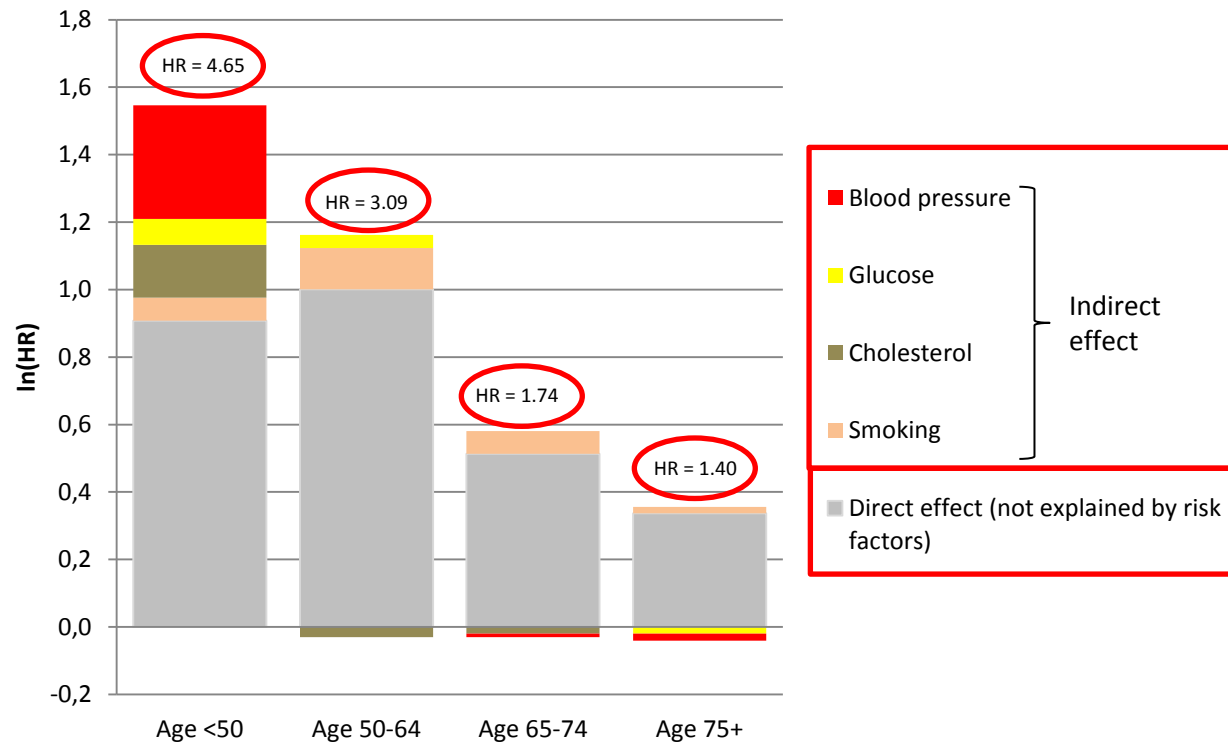
- Can the difference in CHD mortality risk (ICD-10 code I20-I25) between sexes be explained by different risk factor profiles and if yes, how much can be explained?
- Method: Mediation analysis stratified for age groups <50, 50-64, 65-74, and ≥ 75 years based on a Cox regression model for survival data.
- New mediation approach according to Lange et al. which further allows breakdown of indirect effect into single components.
- Lange T, Rasmussen M, Thygesen LC. Assessing natural direct and indirect effects through multiple pathways. Am J Epidemiol. 2014 Feb 15;179(4):513-8.

Results (1)



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Effect decomposition



Results (2)



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Results of mediation analysis: Total, direct, and indirect effects of sex/gender on CHD mortality by age groups, adjusted for age at baseline and year of examination

	<50 years			50-64 years			65-74 years			≥75 years		
Effects (males versus females)	Hazard Ratio	95% CI	Contribution to total effect‡ (%)	Hazard Ratio	95% CI	Contribution to total effect‡ (%)	Hazard Ratio	95% CI	Contribution to total effect‡ (%)	Hazard Ratio	95% CI	Contribution to total effect‡ (%)
Total effect	4.65	3.52 to 6.14†	100.0%	3.09	2.72 to 3.52†	100.0%	1.74	1.56 to 1.93†	100.0%	1.40	1.24 to 1.57†	100.0%
Direct effect*	2.48	1.73 to 3.54	59.1%	2.72	2.37 to 3.12	88.5%	1.67	1.49 to 1.89	93.4%	1.40	1.22 to 1.60	100.5%
Indirect effect, combined	1.87	1.63 to 2.16†	40.9%	1.14	1.10 to 1.18†	11.5%	1.04	1.01 to 1.07†	6.6%	1.00	0.93 to 1.07†	-0.5%
Indirect effect, through systolic blood pressure	1.40	1.26 to 1.55	21.7%	1.00	1.00 to 1.00	0.0%	0.99	0.98 to 0.99	-2.6%	0.98	0.97 to 1.00	-3.2%
Indirect effect, through cholesterol	1.17	1.11 to 1.23	10.0%	0.97	0.95 to 0.98	-3.1%	0.98	0.94 to 1.01	-4.6%	1.00	0.97 to 1.04	1.3%
Indirect effect, through glucose	1.08	1.03 to 1.13	5.0%	1.04	1.03 to 1.05	3.7%	1.00	1.00 to 1.01	0.7%	0.98	0.98 to 0.99	-4.9%
Indirect effect, through smoking	1.07	1.03 to 1.10	4.2%	1.13	1.09 to 1.17	10.8%	1.07	1.03 to 1.12	13.1%	1.02	0.97 to 1.08	6.2%

*Effect of sex/gender not mediated by the four analyzed risk factors. †Calculated according to the Delta-method. ‡On ln HR scale.

Take home messages



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- Premature mortality from CHD is substantially lower in women.
- We estimated the contribution of major risk factors to this gender difference.
- BP and TC explain one third of the survival benefit in premenopausal women.
- This is in line with the oestrogen hypothesis.
- In older persons, risk factors contribute much less to the mortality difference.