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Mediation analysis of the relationship between sex, cardiovascular risk factors and mortality from coronary heart disease: Findings from the population-based VHM&PP cohort

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ABSTRACT

Background: In Europe, annually about 77,000 women, but 253,000 men die prematurely from coronary heart disease (CHD) before the age of 65 years. This gap narrows with increasing age and disappears after the eighth life decade. However, little is known regarding the contribution of cardiovascular risk factors to this sex difference.
Objective: We investigated to what extent men's higher risk of dying from CHD is explained through a different risk factor profile, as compared to women.
Methods: Mediation analysis technique was used to assess the specific contributions of blood pressure, cholesterol, glucose, and smoking to the difference between men and women regarding CHD mortality in a large Austrian cohort consisting of 117,264 individuals younger than 50 years (as a proxy for pre-menopausal status) and 54,998 older ones, with 3892 deaths due to CHD during a median follow-up of 14.6 years.
Results: Adjusting for age and year of examination, we observed a male versus female CHD mortality hazard ratio (HR) of 4.7 (95% CI: 3.4–5.9) in individuals younger than 50 years, of which 40.9% (95% CI: 27.1%–54.7%) was explained through risk factor pathways, mainly through blood pressure. In older participants, there was a HR of 1.9 (95% CI: 1.8–2.0) of which 8.2% (95% CI: 4.6%–11.7%) was mediated through the risk factors.
Conclusion: The extent to which major risk factors contribute to the sex difference regarding CHD mortality decreases with age. The female survival advantage was explained to a substantial part through the pathways of major risk factors only in younger individuals.

1. Introduction

Coronary heart disease (CHD) is the leading cause of death in most industrialized countries [1]. CHD incidence rates increase with age, however to a varying extent in males and females. At younger ages, incidence and mortality rates are markedly lower in women, whereas with increasing age the gap narrows. There is a lag effect of approximately ten years, i.e. the incidence rate of 65 year old women is comparable to that of 55 year old men [2]. By the eighth decade, the difference between both sexes is nearly absent [3,4]. In Europe, per year approximately 77,000 women (corresponding to 1.8% of all deaths), but 253,000 men (corresponding to 5.7% of all deaths) die prematurely from CHD before the age of 65,

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while, when considering all ages, slightly more women do so than men (903,000 versus 876,000) [4].

There are indications that naturally occurring female sex hormones, like oestrogen, may offer protection against CHD in premenopausal women, causing the delayed risk increase with age in women [5]. However, the Women's Health Initiative trial showed that oestrogen administration did not protect women against CHD [6]. Recent research provides evidence that endogenous and exogenous testosterone is affecting the risk of CHD [7].

There are substantial differences between men and women regarding the profiles of some cardiovascular risk factors, which may mediate parts of the observed sex difference [5,8–10]. For example, total cholesterol (TC) values are on average lower in younger women, but while these values reach a peak level for men around the age of 60 years, values keep increasing as women get older. Eventually, at older ages women are the ones with higher TC levels [11]. Furthermore, smoking habits are still less favourable for men in most countries, although women are catching up [12,13]. Hypertension and hyperglycaemia show less consistent age-related sex patterns [9].

While there have been studies investigating the possible different role of cardiovascular risk factors in men and women [8,14,15], there have not yet been, to our knowledge, any attempts to explore how much of the sex effect is mediated through risk factors. For other exposures, mediation analysis has indeed been performed, for example for overweight [16–18]. In these studies, the amount mediated by risk factors was assessed by examining the change in risk measures estimated in models with and without the mediators, an approach first introduced by Baron and Kenny [19].

Meanwhile, it has been shown that the Baron and Kenny method works well in the special case of linear models without interactions, but is mathematically inconsistent otherwise [20,21]. In Cox regressions, the underlying baseline hazard functions might be different in the two models, rendering a comparison problematic [21]. Thus, to investigate mediation effects for time-to-event outcomes another approach is preferable. Until recently, mediation analysis of this kind was tedious. Lange et al. however developed a simplified approach [20,22], based on marginal structural models, and extended the framework to also encompass multiple mediators [23]. With this approach, for the first time, the mediated risk can be broken down to factor level, e.g. the question “How much of the difference in CHD risk between men and women is mediated by the TC pathway?” can be answered directly.

To our knowledge, despite the advantages of the new framework, the method of Lange et al. has only been applied once in the field of coronary heart disease, actually with education and risk factors [24]. We used this model to elucidate to what extent men's higher risk of dying from CHD is mediated by a different risk factor profile, as compared to women. Specifically, we investigated the influence of sex on the time-to-event outcome “death due to CHD” and which proportion of the total sex effect is mediated through the risk factors systolic blood pressure, TC, glucose, and smoking status (see Fig. 1).

2. Materials and methods

2.1. Data source and study population

The Vorarlberg Health Monitoring and Promotion Programme (VHM&PP) is one of the world's largest ongoing population-based risk factor surveillance programmes. The cohort was initiated in 1985 and is conducted by the Agency for Social and Preventive Medicine in Vorarlberg, the westernmost state of Austria. Between 1985 and June 2005, 99,894 female and 85,473 male Vorarlberg residents (aged older than 18 years) were enrolled in the VHM&PP. Approximately two thirds of the adult population of the region have participated in the programme. Measurements of height, weight, blood pressure, TC, blood glucose, and smoking status were routinely obtained by trained physicians under standardized conditions including an overnight fast. Data on date and cause of death was provided by the regional health authority and was linked to the VHM&PP database through a validated record linkage procedure [25]. High autopsy rates in Austria, especially among younger individuals [26], guarantee high quality of death cause information. A more detailed description of the programme is reported elsewhere [11,27].

Since blood glucose was measured under fasting conditions only from 1989 onwards, we excluded participants with no visit after 1988 from our analyses (n = 11,842, 6.4%). Furthermore we excluded 1263 participants (0.7%) with missing or incomplete data on the investigated cardiovascular risk factors, resulting in a total of 92,873 women and 79,389 men eligible for analyses in the current investigation. Median follow-up time of this population was 14.6 years.

By the end of 2009, 17,962 deaths were recorded of which 3892 (21.7%) (2106 in men, 1786 in women) were due to coronary heart disease (CHD) including acute, subacute and chronic forms. CHD was defined via the following codes of the International Classification of Diseases, 9th & 10th Revision (ICD-9, ICD-10): ICD-9 410 to 414 and ICD10 I20 to I25.

For our investigation, institutional review board approval was obtained by the Ethics Committee of the state of Vorarlberg and the study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

2.2. Statistical analysis

Study participants' characteristics and risk factor measurements were analysed descriptively (mean and standard deviation (SD) for continuous, and counts and percentages for categorical data) and compared with Fisher's exact tests and t-tests between men and women using a two-sided significance level of $\alpha = 0.05$.

Mediation analysis was performed using the approach proposed by Lange et al. [22,23] which is based on marginal structural models. This approach offers a tool to decompose the total effect of a given exposure into a natural direct effect and a natural indirect effect through one or several mediators. The natural direct effect compares CHD mortality in men with that in women if risk factor levels for men were set to the levels which would have been observed if they had been women. Detailed definitions of these effects have been described elsewhere [20,28]. Fig. 1 shows the underlying model of our analysis. It assumes a causal relationship between selected risk factors and CHD outcome which is well established [29].

Year of examination and individuals' age were included in the models to adjust for confounding of the sex-mediator, sex-CHD, and mediator-CHD associations. Estimates of the direct and indirect effects were obtained from weighted Cox proportional hazards models for the outcome death due to CHD. For determining the weights needed in the Cox model, we regressed the mediators TC, glucose, and systolic blood pressure on sex, year of examination, and age with linear models, and the mediator smoking status on sex, year of examination, and age with a binomial logistic model. We also checked the assumption that each mediator is independent of the others conditional on sex and confounders in separate models [23].

The contribution of direct and indirect effects to the total sex effect was calculated on the ln(HR) scale since effects are additive