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Risk Factors for Heart Failure: A Population-Based Case-Control Study

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Abstract

Background—The relative contribution of risk factors to the development of heart failure remains controversial. Further, whether these contributions have changed over time, or differ by sex is unclear. Few population-based studies have been performed. We aimed to estimate the population attributable risk (PAR) associated with key risk factors for heart failure in the community.

Methods—Between 1979 and 2002, 962 incident heart failure cases in Olmsted County were age and sex-matched to population-based controls using Rochester Epidemiology Project resources. We determined the frequency of risk factors (coronary heart disease, hypertension, diabetes mellitus, obesity, and smoking), odds ratios and PAR of each risk factor for heart failure.

Results—The mean number of risk factors for heart failure per case was 1.9 ± 1.1 , and increased over time ($p < 0.0001$). Hypertension was the most common (66%), followed by smoking (51%). The prevalence of hypertension, obesity, and smoking increased over time. The risk of heart failure was particularly high for coronary disease and diabetes with odds ratios (95% confidence intervals) of 3.05 (2.36–3.95) and 2.65 (1.98–3.54), respectively. However, the PAR was highest for coronary disease and hypertension; each accounted for 20% of heart failure cases in the population, though coronary disease accounted for the greatest proportion of cases in men (PAR 23%) while hypertension was of greatest importance in women (PAR 28%).

Conclusions—Preventing coronary disease and hypertension will have the greatest population impact in preventing heart failure. Sex-targeted prevention strategies may confer additional benefit. However, these relationships may change, underscoring the importance of continued surveillance of heart failure.

Keywords

heart failure; epidemiology; risk factors

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INTRODUCTION

Population-based studies have investigated the heart failure epidemic. In the Framingham Heart Study¹ and in Olmsted County², the incidence of heart failure has remained stable or decreased over time while survival improvements were limited and diverged by sex, with greater survival gains in men than women. The explanations for these disparities are lacking and could be related to differences in the risk factors for development of heart failure.

The relative contribution of various risk factors to the development of heart failure remains controversial and has seldom been investigated in population-based studies^{3–7}. In the Framingham Heart Study, hypertension contributed a large portion of heart failure cases, particularly in women⁶. Further, obesity was associated with a doubling of the risk of heart failure, and was responsible for an estimated 14% of heart failure cases in women and 11% in men⁷. However, data from the National Health and Nutrition Epidemiologic Survey (NHANES) suggested that coronary heart disease had the largest impact on the development of heart failure, and may be responsible for more than 60% of cases. These important findings were derived from Framingham and NHANES participants enrolled starting in the 1970s. Consequently, these data may not be applicable to different cohorts or time periods where the burden of risk factors may differ. This underscores the importance of examining the risk of heart failure conferred by various conditions among different populations including more contemporary cases.

We aimed to address these gaps in knowledge and to evaluate the contribution of coronary disease, hypertension, diabetes mellitus, obesity, and smoking to heart failure. This population-based case-control study was undertaken to determine the frequency of risk factors for heart failure among incident cases, how these frequencies may have changed over time and to estimate the population attributable risk (PAR) for each risk factor for heart failure.

METHODS

Study Population

Olmsted County, Minnesota has an estimated population of 137,521 (2006 US Census), with 50.4% females. Epidemiologic research is possible because the county is isolated from other urban centers, and medical care is delivered to local residents by few providers⁸. Through the Rochester Epidemiology Project, the medical records from all sources of care used by the population are linked, providing a unique infrastructure to analyze disease determinants and outcomes. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Selection of Cases and Controls

Case subjects were Olmsted County residents with a first diagnosis of heart failure from 1979–2002. Potential case subjects were identified by International Classification of Diseases, Ninth Revision (ICD9) code 428 (heart failure). A subset was randomly selected for validation and data abstraction. The index date was defined as the first evidence of heart failure in the medical record. Cases were validated using methods previously described². Briefly, nurse abstractors reviewed records to ensure each met Framingham criteria⁹ and had a physician's diagnosis of heart failure. When this method was utilized previously², missing data were minimal and Framingham criteria could be applied in 98% of cases. The inter-abstractor agreement was 100%, indicating these methods are highly reproducible.

Control subjects were selected from the Olmsted County population. In any three-year period, over 90% of residents are seen at Mayo Clinic^{8,10}. Thus, the Rochester Epidemiology Project provides a virtually complete enumeration of the population from which we selected controls.

Information on exposures prior to the index date was obtained from the medical record. This approach avoids many biases common with case-control studies including differential recall, non-response bias, and survivor bias.

Control subjects were matched to each case subject by age (± 3 years) and sex. The index date for the control corresponds to the incidence date of the matched heart failure subject. Among eligible controls, we selected those with the closest clinic registration numbers to the cases, which matches them for their medical record duration to ensure similar opportunities for care. Control subjects were sampled without replacement. Controls with heart failure prior to the index date were excluded.

Risk Factors

The occurrence of each risk factor (coronary disease, hypertension, diabetes, obesity, smoking) was collected from age 18 (or date of emigration to Olmsted County thereafter) until the date of incident heart failure or index date for controls. Myocardial infarction was ascertained using standardized criteria¹¹. Coronary disease was defined as a prior myocardial infarction or revascularization (coronary bypass surgery or angioplasty). Hypertension was defined by physician diagnosis or systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg. Diabetes was defined by fasting blood glucose levels or use of insulin and/or oral hypoglycemic medications. Body mass index (BMI, kg/m^2) was calculated using the weight and earliest adult height. Obesity was defined as BMI of $30.0 \text{ kg}/\text{m}^2$ or greater. The date when patients first fulfilled criteria for the diagnoses of coronary disease, hypertension, diabetes, or obesity was used as the diagnosis date. Smoking status was defined as 'never' or 'ever'; heavy smoking was defined as >20 pack-years.

Statistical Analysis

Differences in the prevalence of risk factors by sex were examined using a χ^2 test; trends over time were compared by year of heart failure diagnosis (1979–84, 1985–90, 1991–96, 1997–2002) with the Mantel Haenszel χ^2 test. Differences in the time from onset of risk factor to heart failure by sex were tested using linear regression adjusting for age.

To account for the case-control design, a matched analysis was performed with conditional logistic regression. A model was developed to estimate the odds ratio (OR) of heart failure associated with each risk factor. To determine whether risk of heart failure differed by sex, an interaction term exposure*sex was included in each model. The PAR represents the proportion of all cases in the target population that is attributable to the exposure. It may be estimated from a case-control study if the exposure rate in the control group is representative of the population, as is the case here due to our population-based selection of controls. PAR estimates and confidence intervals were provided via software from the Mayo Clinic Division of Biomedical Statistics and Informatics^{12,13}. The PAR was estimated for each risk factor, and a summary PAR for all five risk factors was generated to account for overlapping risk. Pack-years was not available for 13% of smokers; other missing data were $<3\%$ for any variable in the analyses. A p value <0.05 was used as the level of significance. Analyses were performed using SAS 8.2 (SAS Institute Inc., Cary, NC) and S-PLUS 8.01 (TIBCO Software, Palo Alto, CA).

RESULTS

Study Population

The study included 962 heart failure subjects (mean age of cases 75.4 years; 53.7% women). Women were older than men (mean age 78.3 years versus 72.1 years, $p<0.001$). By definition, the 962 controls had a similar age and sex distribution.

Frequency of Heart Failure Risk Factors Among Case Subjects

Hypertension was most common, followed by smoking (Table 1). Among ever smokers, 24.0% were light smokers, while 76.0% were heavy smokers. The mean number of heart failure risk factors per case subject was 1.9 ± 1.1 ; 29.4% had 1, 62.0% had 2 or more, while only 8.6% had none. The prevalence of risk factors by sex was similar for diabetes and obesity, but men had a greater frequency of coronary disease and smoking, while women had a greater frequency of hypertension. The number of risk factors per heart failure case increased over time with mean risk factors of 1.61, 1.89, 1.98, and 2.13 from 1979–84, 1985–90, 1991–96, and 1997–2002, respectively (p for trend <0.001). The prevalence of hypertension, obesity, and smoking increased over time (Table 2). While the proportion of patients who had ever smoked prior to heart failure diagnosis increased over time, the proportion of current smokers at the time of diagnosis declined (17%, 20%, 15%, and 12% from 1979–84, 1985–90, 1991–96, and 1997–2002, respectively).

Time from Exposure to Development of Heart Failure

The duration of exposure prior to heart failure differed according to the risk factor. Heart failure developed only a few years after coronary disease diagnosis, contrasting with longer durations of exposure for other factors (Table 3). After adjusting for age, women developed heart failure more rapidly after being diagnosed with coronary disease than men. While men tended to develop heart failure more quickly after being diagnosed with hypertension or diabetes, the results were not significant ($p=0.10$ for hypertension, $p=0.08$ for diabetes).

Risk of Heart Failure According to Risk Factor

The risk of heart failure associated with each exposure and the PARs are presented in Table 4. A history of coronary disease was associated with the greatest risk, followed by diabetes. While ever smoking was associated with an increased risk of heart failure (OR 1.37, 95% CI 1.13–1.68), when stratified by smoking burden, heavy smoking was associated with greater risk (OR 1.87, 95% CI 1.46–2.39) than light smoking (OR 1.02, 95% CI 0.74–1.40). There was no sex differences in the association between each risk factor and the development of heart failure (exposure*sex interaction term $p>0.20$ for all). The PARs were highest for coronary disease and hypertension, with each accounting for 20% of heart failure cases. Despite the weaker association between hypertension and heart failure relative to other factors, the PAR was high given its high prevalence. In women, hypertension had the highest PAR of the risk factors examined (28%), followed by coronary disease (16%). In men, coronary disease was responsible for the highest proportion of cases (PAR 23%), followed by smoking (22%). We examined whether the PAR for each risk factor changed over time. There was no evidence for a change for coronary disease, diabetes, and smoking. By contrast, the PAR for hypertension increased from 15% (1979–84) to 29% (1979–02), and for obesity from 8% (1979–84) to 17% (1997–02). These differences did not reach statistical significance. After adjusting for the risk associated with all five risk factors, the summary PAR was 52%. This suggests that these five risk factors are responsible for 52% of incident heart failure cases in the population.

DISCUSSION

This population-based study indicates that coronary disease, hypertension, diabetes, obesity, and smoking commonly precede the development of heart failure in both men and women. The risk of heart failure is greatest for coronary disease and diabetes, while coronary disease and hypertension are responsible for the largest proportion of new heart failure cases in the population. Sex differences in the etiology of heart failure may exist, with hypertension playing the greatest role in women and coronary disease in men. However, as the burden of obesity increases, the etiology of heart failure may continue to evolve.

Risk Factor Prevalence

Hypertension was most common among incident heart failure cases, occurring in 66% of patients. In the Framingham Heart Study, hypertension predated heart failure in 91% of cases⁶, though prevalence rates in the Cardiovascular Health Study were similar to ours⁵. Our findings extend previous reports by examining the time from onset of each risk factor to heart failure diagnosis. While the onset of hypertension or obesity preceded heart failure by an average of more than 10 years, heart failure occurred much more rapidly after coronary disease. This is consistent with the known pathologic mechanisms for coronary disease development according to each risk factor. For coronary disease, sudden cardiac events such as a myocardial infarction may lead quickly to cardiac dysfunction¹⁴ and heart failure. Conversely, hypertension, diabetes, and obesity may lead to heart failure over longer durations via myocardial metabolic dysfunction¹⁵, oxidative stress¹⁶, and endothelial dysfunction¹⁷, leading to left ventricular remodeling^{18,19} and cardiac dysfunction.

The burden of all risk factors among heart failure cases increased over time, with significant increases for hypertension, obesity, and smoking. While an increase in the prevalence of diabetes and obesity in the U.S. population and in heart failure patients has been described^{20–23}, trends in the prevalence of coronary disease and hypertension are less consistent. Framingham data demonstrated large increases in the prevalence of coronary disease among heart failure patients²³. However, a decrease in coronary disease deaths in the U.S. general population in recent years has been reported^{24,25}, and Olmsted County data suggest coronary disease incidence has decreased in a similar time frame^{26,27}. Our findings indicate that the proportion of patients with coronary disease prior to heart failure is stable or increasing. This could reflect improved survival among persons diagnosed with coronary disease over time^{28,29}, leading to patients living longer to develop heart failure. Some studies indicate that heart failure after myocardial infarction may be declining³⁰, but an aging population and increasing number of myocardial infarction survivors yields a greater number of persons at risk.

Among Framingham participants, a decline over time in hypertension prior to heart failure diagnosis was noted²³. In contrast, these data suggest that hypertension prior to heart failure had increased. This is consistent with NHANES data, which demonstrated a 10% increase in hypertension from 1990–2000³¹, and data from hospitalized heart failure patients at Mayo Clinic³². Further, hypertension awareness and control remain suboptimal³³. The increasing burden of risk factors among heart failure cases underscores the need for targeted risk factor prevention and management in the population.

Population Attributable Risk

Both the prevalence of the risk factor and its associated risk for the outcome are needed to determine the population impact of a risk factor on a disease. Coronary disease, hypertension, diabetes, obesity, and smoking were each associated with an increased risk for heart failure, but the PAR was greatest for coronary disease (20%) and hypertension (20%). Prior population-based studies have shown differing results, with Framingham demonstrating a larger PAR for hypertension (39% male, 59% female) than myocardial infarction (34% male, 13% female)⁶, while PAR were similar in the Cardiovascular Health Study (13% each)⁵, and the PAR was greater for coronary disease (62%) than hypertension (10%) in NHANES⁴. This could be partially related to differences in definitions. For instance, coronary disease was defined by self-report in NHANES⁴, whereas the Framingham definition of MI only included a validated event during hospitalization or using electrocardiographic criteria⁶. We defined hypertension based on current guidelines³⁴, and coronary disease was validated. Though the PAR overall was equal for hypertension and coronary disease herein, hypertension was the primary risk factor for heart failure in women, while coronary disease had the greatest impact in men. This

is partially attributable to differences in the prevalence of risk factors by sex; hypertension being more common in women prior to heart failure, while coronary disease is more common in men. The increasing burden of hypertension among the population, and women in particular, may contribute to the escalating role of diastolic heart failure in the community³². These data underscore that improved prevention of coronary disease and hypertension in the population may lead to the greatest reduction in the incidence of heart failure. Further, sex-specific prevention strategies may offer additional benefit.

The combined PAR for the risk factors examined was 52%, indicating that coronary disease, hypertension, diabetes, obesity, and smoking are responsible for 52% of incident heart failure cases in the population. Significant overlap in risk factors and their influence on heart failure exist, as the total PAR of 52% is less than the sum of each PAR. Some of the etiologies examined lie in the causal pathway for others. For example, diabetes and smoking are established risk factors for coronary disease³⁵. However, a significant proportion of the population risk of heart failure may be due to unmeasured factors. While the potential etiologies of heart failure are diverse and numerous³⁶, we recognize that factors including valvular disease and renal dysfunction may also lead to heart failure.

Limitations

Some limitations should be acknowledged to aid in data interpretation. Rare heart failure risk factors were not explored. Risk factors were ascertained by medical record review, which may lead to under-recognition, but should not differ between cases and controls. Since the study population was mainly Caucasian, these data need replication in other racial and ethnic groups. Finally, we used a case-control design, the associated biases are largely minimized by use of population-based controls and incident heart failure cases. However, the inclusion of a large number of population-based heart failure cases over a prolonged time period is a notable strength. Further, each case subject was followed via their medical record for an average of 40 years prior to heart failure, allowing identification of risk factors at onset.

Conclusions

While advances in medical therapies have led to improvements in survival after heart failure diagnosis, prognosis remains poor^{1,2,37}. The best strategy for avoidance of morbidity and mortality from heart failure is prevention. The present study has important public health implications, and suggests that targeting prevention of hypertension and coronary disease may have the greatest impact on reducing the number of heart failure cases in the population. However, as the relative contribution of risk factors to the development of heart failure in the population continues to evolve, ongoing surveillance is important to maintain accurate preventive efforts.

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Table 1

Prevalence of Risk Factors Among Heart Failure Cases 1979–2002

Risk Factor	Prevalence Among Cases (%)		
	Overall (n=962)	Women (n=517)	Men (n=445)
Coronary heart disease	29.1	21.1	38.4 [*]
Hypertension	66.2	72.7	58.6 [*]
Diabetes	18.5	16.8	20.5
Obesity	24.5	23.2	26.1
Ever smoker	51.2	33.7	71.6 [*]

*
p<0.001 compared with prevalence among females; all other p>0.05

Change in Prevalence of Risk Factors over Time Among Heart Failure Cases 1979–2002

Table 2

Risk Factor	Year of Heart Failure Diagnosis (% Patients)				P value (trend)
	1979–1984	1985–1990	1991–1996	1997–2002	
Coronary heart disease	25.0	30.3	28.5	33.0	0.097
Hypertension	58.4	65.5	67.6	73.6	<0.001
Diabetes	13.0	20.9	20.8	19.4	0.085
Obesity	19.6	20.5	28.4	29.5	0.003
Ever smoker	45.6	51.5	50.2	57.8	0.012

Table 3

Time from Risk Factor to Development of Heart Failure Among Cases

Risk Factor	Time From Risk Factor to Heart Failure Diagnosis (years), median (25 th –75 th percentile)		
	Overall (n=962)	Women (n=517)	Men (n=445)
Coronary heart disease	4.9 (0.4, 10.8)	3.3 (0.2, 8.2)	5.7 (0.9, 12.3) *
Hypertension	15.1 (7.3, 23.7)	16.0 (7.9, 26.1)	13.4 (6.8, 20.8)
Diabetes	9.8 (5.0, 18.6)	12.6 (5.7, 20.0)	8.5 (4.1, 16.0)
Obesity	16.1 (10.1, 20.4)	16.2 (10.7, 20.1)	16.0 (8.4, 20.5)

* Age-adjusted p<0.05 compared with women

Table 4
Association Between Heart Failure and Risk Factors From Case/Control Analysis

Risk Factor	Odds Ratio (95% CI)	P value	Population Attributable Risk (95% CI)	
			Women	Men
Coronary heart disease	3.05 (2.36–3.95)	<0.001	0.16 (0.12, 0.20)	0.23 (0.16, 0.30)
Hypertension	1.44 (1.18–1.76)	<0.001	0.28 (0.14, 0.42)	0.13 (0.00, 0.26)
Diabetes	2.65 (1.98–3.54)	<0.001	0.10 (0.06, 0.14)	0.13 (0.08, 0.18)
Obesity	2.00 (1.57–2.55)	<0.001	0.12 (0.07, 0.17)	0.13 (0.07, 0.19)
Ever smoker	1.37 (1.13, 1.68)	0.002	0.08 (0.00, 0.15)	0.22 (0.07, 0.37)

CI= confidence interval