

Predicting Coronary Heart Disease through Risk Factor Categories

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Abstract – The primary objective of this study was to examine whether accurate prediction of coronary heart disease (CHD) in undiagnosed individuals is possible through risk factor evaluation, mainly through 4 governing factors; behavior, condition, age and gender. The secondary objective was to improve currently used coronary prediction algorithms or programs by including new factors discussed here. To evaluate the impact of risk factors in predicting CHD, a meta-analysis was performed by reviewing published data from various randomized trials and studies. The results show that the mentioned factors are accurate predictors of CHD and that there is a drastic need to improve existing risk-factor evaluating programs or algorithms by including other factors, mainly central obesity. These findings are important in managing CHD related deaths worldwide. Ability to predict CHD will reduce both mortality and the long-term expenses associated with the management of the disease.

Keywords— coronary heart disease, risk factors, prediction algorithms, management of CHD

INTRODUCTION

Over the past decade coronary heart disease (CHD), also known as ischemic heart disease or atherosclerotic heart disease, has been the leading cause of death in both developed and developing nations with persistently rising incidence [1, 2]. The majority of the burden is tilted towards low and middle-income countries [3]. CHD is caused by plaque accumulation within the coronary arteries, reducing blood flow, hence nutrient and oxygen supply, to cardiac muscles. Heart failure (HF), an end result of CHD, can be considered an epidemic in the United States of America with over 5 million people being affected and over 500,000 newly diagnosed cases every year [4]. Though there has been a relative improvement in 5 year survival of such patients due to advancement in therapy, the prognosis remains poor [5, 6]. The dire situation is aggravated by the fact that CHD treatment is chronic, expensive and may require frequent hospitalization [7]. There are several factors that have been established as risk factors for CHD. These include age, gender, diabetes, hypertension, etc [8]. The irony to all of this is that both death and disability resulting from

CHD is preventable if the modifiable risk factors are properly identified and corrected [9]. Cardiovascular epidemiology commenced in the 1930s in the United States due to observable changes in mortality [10].

RESEARCH METHOD

In the research presented here in order to properly evaluate the impact of each factor or sub-division, a meta-analysis was performed by reviewing several literatures from known medical websites or journals to gather the various risk factor categories to link to CHD. Among the various research methods used to identify risk factor categories the most common one is the cohort studies and other ways include systemic reviews, qualitative research filters, etc. A lot of times a combination of research methods have also been used in finding better results. The descriptions of various risk factors include how HDL cholesterol level was assayed, how diabetes causes CHD, how smoking, age, gender, even menopause in women can be a risk factor in heart diseases. The risk factors were divided into 4 main segments; behavior, gender, condition and age. Each factor contained 2 or more sub-divisions.

Goal

Evaluating both classical and potential risk factors to properly predict development of CHD among individuals who have not been previously diagnosed.

Factor 1 (Behavior)

F1: The behavioral category in the model is responsible for the prediction of CHD includes the three common factors: i. Smoking, ii. Alcohol consumption and iii. Stress leading to depression.

i. Smoking: Major factor for cardiovascular disease is smoking and use of other forms of tobacco. Even at the lowest levels of exposure the effect of cigarette smoking on cardiovascular health is evident but the adverse effects of

smoking are reversible if smoking is ceased with cardiovascular risk decreasing substantially within the first 2 years^[8, 16]. It is cost effective as well. Smoking causes decreased coronary blood flow and myocardial oxygen delivery and has adverse effects on lipids, blood pressure, and insulin resistance and also cause biochemical changes to the endothelium.

ii. Alcohol Consumption: The effect of alcohol is highly contradictory. Meta-analysis performed by Beulens and colleagues have proved that moderate consumption of alcohol (one or two drinks a day) is actually beneficial in reducing deaths related to CHD, compared to abstainers. This is because at moderate dose, alcohol increases levels of HDL-C, hence, thinning blood^[27]. The mechanism through which it performs this is yet unknown. However, heavy drinkers are more prone to have cardiac problems when compared to non-alcoholics. Heavy drinking (≥ 300 g ethanol/week or more than 3 drinks a day), was associated with increased risks of total, hemorrhagic and ischemic strokes, while moderate alcohol consumption was not associated with risk of CHD. At high doses, alcohol increases blood pressure and also contributes to platelet coagulation and increased fibrinolysis which eventually leads to ischemic stroke.

iii. Stress and Depression: An increased risk of cardiovascular diseases and the risk of stroke are associated with difficulty in managing psychological stress. From severe stress people can get into depression which is more found in CHD patients using antidepressants than general populations. TCA antidepressants are reported to cause increased risk of CHD. Spousal caregivers (irrespective of gender) for cancer patients have significantly increased risks for developing CHD or ischemic strokes, particularly for terminal cancer patients^[24].

Factor 2 (Condition)

F2: The second category in the model is Condition which includes six different factors playing roles in CHD.

i. Blood Pressure: This can be considered as one of the primary or classical risk factors as it has already been established in several studies as a risk factor long ago^[28]. Build-up of fatty deposits or plaque on the inner walls of the coronary arteries (atherosclerosis) decreases the lumen diameter, hence, increases blood pressure and restricts the flow of blood to the heart. If left untreated, angina occurs and eventually heart failure. There are two types of hypertension, primary and secondary. Primary hypertension caters to 90-95% of all cases of HT and there is no identifiable cause, though genetics, stress, lifestyle and dietary intake have been regularly indicated^[29]. Secondary hypertension is caused by an underlying condition, which includes renal disease, endocrine disease and tumor along with the previously mentioned factors for primary HT. Effects of HT are also age-dependent as each increment of 20 mm Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure doubles the risk of CHD across the entire range of blood pressure from

115/75 to 185/115mm Hg for individuals aged between 40-70 years^[30].

ii. Obesity: Though it contributes to premature mortality from all causes of death including CHD^[23], obesity is still the most undermined factor, evident by the fact that it is not included in standard risk assessment systems such as FRS. This is mainly because of the several inaccuracies in measuring obesity^[23]. Studies conducted by Dhaliwal & Welborn in major Australian cities have confirmed central obesity as an accurate indicator for developing CHD. Central obesity was assessed by measuring waist circumference (WC) and waist-to-hip ratio (WHR) using standardized procedures^[31, 32] and meta-analysis revealed both measurements to be strong indicators of CHD deaths, even in subjects at lower levels of Framingham risk scores^[33]. Receiver operator characteristic (ROC) curves for WHR plus smoking and Framingham prediction model were identical in predicting CHD deaths^[9], confirming the role of obesity as a key contributor to CHD-related deaths.

iii. Cholesterol level: Another classical risk factor, the Framingham Heart Study and other similar epidemiological studies proved long ago the deadly association between blood-cholesterol levels or blood LDL-C levels and CHD^[34, 35]. Though, LDL-C is the principal lipid-carrier protein^[14], accumulation of it in blood results in their subsequent oxidation, followed by engulfment by macrophages via protein expression, forming plaque and leading to atherosclerosis^[36]. Most of the current anti-hypertensive regimens mainly focus on reducing the LDL-C levels in plasma and the efficacy of these lipid lowering agents in reducing CHD related mortality have been illustrated in various clinical trials^[37, 38]. However, these benefits are age-dependent^[39]. On the contrary, high-density lipoprotein cholesterol (HDL-C) have been shown to directly oppose atherosclerosis by removing cholesterol from foam cells, by inhibiting the oxidation of LDLs, and by limiting the inflammatory processes that underlie atherosclerosis^[36]. An approximate 1 mg/dL increase in HDL level decreases coronary risk by 2% in men and 3% in women^[40]. As a result, increasing blood HDL-C levels has been employed as a strategy to reduce CHD mortality^[41].

iv. Diabetes: Diabetes mellitus patients have a 2-3 fold increased chance of suffering from CHD,^[42] the effect being more pronounced in women than men^[43]. Diabetes is normally associated with the symptoms of hypertriglyceridemia, low HDL-C plasma levels, obesity and hypertension, all of which are factors governing CHD occurrence^[44] and the Framingham Study also suggested hyperglycemia to be an independent risk factor^[45, 46]. Though the exact mechanism is still not properly understood, insulin resistance has been suggested as a common mechanism for these factors^[47]. Once CHD has developed, frequency of cardiac complications drastically increase, morbidity and mortality rates are significantly higher in diabetic CHD patients than their non-diabetic counterparts^[48]. Improved glycemic control is coherent with reduced micro-vascular complications of diabetes^[49].

v. Genetics: As several of the risk factors can be hereditary, such as diabetes, obesity and hypertension, the role of genetics in the development of CHD has always been heavily but only indirectly applied. People born with cardiac disorders such as hypertrophic cardiomyopathy (enlarged muscles of the left ventricle) or polymorphism in metabolic enzymes, glucose metabolism, etc may contribute to CHD. Family history contributes significantly to CHD incidences [8]. Ethnic variation is present in CHD mortality outcomes, as proved by Eaton and colleagues. Analysis of patient records from over 40 centers showed that Black women had the highest age-standardized incidences of HF (380 in 100,000 person-years), followed by Caucasians, Asians and Hispanics [25]. Death of a person whose twin died of CHD complications between the age 36-55years was 10 times greater than one whose twin did not die of CHD, relative risk remains unchanged for twins aged older than 85 years [50]. A genomic profile constructed of highly validated genetic variants from genome-wide association studies was created by Tikkanen and colleagues, and the genetic risk score (GRS) was highly associated with incident CV disease even after adjustment for traditional risk factors during 10 to 20 years of follow-up [51], thus scientifically cementing genetics as a direct risk factor for CHD.

vi. Menopause in women: Studies show that compared to men of similar age and postmenopausal women, incidences of CHD is significantly lower in premenopausal women, suggesting the idea of the effects of endogenous estrogen in preventing atherosclerosis [52, 53, 54]. Estrogens have shown to have an acute vasodilatory effect on the vessel wall and inhibit of smooth-muscle cell proliferation [55]. Studies have indicated that hormone replacement therapy (HRT) has beneficial effects on CHD [56] while others like the HERS trial claim that it has no significant role in reducing CHD mortality in postmenopausal women [57]. Schierbeck and colleagues proved successfully that after 10 years of randomized treatment, women receiving hormone replacement therapy early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer, venous thromboembolism, or stroke [58]. Further research needs to be conducted to confirm these finding.

Factor 3 (Age)

F3: The third category chosen is age which is subdivided into three sections. The detrimental effect of age has already been explained, as the negative impact of the other factors, such as diabetes, hypertension, hypercholesterolemia, etc increases steadily with increasing age.

i. Young age: As indicated earlier, premenopausal women (< 40yrs) run significantly lower risks in developing CHD than postmenopausal women [52, 53, 54]. The scenario is similar in men. Kasser and Bruce proved that young, normal men (>=25 yrs) ran the least risk of CHD compared to older men struck

as they demonstrated duration of exertion and maximal exercise heart rate while minimal systolic pressure [59].

ii. Middle age: Middle-aged men and women (between 40-65 years) show greater risks for developing CHD than younger ones, but less than older counterparts, due to the greater incidences of co-morbidities such as hypertension and diabetes. Though in general the risk for CHD doubles for every 10mm Hg rise in blood pressure for individuals between 40-70 years [30], isolated systolic hypertension is steeper for women >= 55years, tilting the risk towards women [28]. Effects of hyperaldosteronism, leading to secondary hypertension, are more pronounced in this age group [60].

iii. Older age: Elderly people (>=65 years) are normally associated with high incidences of CHD and HF, resulting in the steep mortality rates of CHD [1, 2]. The risks for hypertension are the greatest [30] along with the hazards of diabetes mellitus, evident by the fact that most diabetic patients die of CHD [61].

Factor 4 (Gender)

F4: The fourth risk factor is the gender difference and how the effect of CHD varies on them. CHD is a threat for both the genders.

i. Male: Traditionally, CHD has been considered predominantly affecting men [8]. As a result, most of the risk factors or discoveries established regarding CHD over the years have been through extensive cardiovascular research conducted on male patients [8]. Extensive research on women initiated during the 1990s, all of which later confirmed the greater female susceptibility to CHD [8, 28, 43].

ii. Female: Risk factors like low high-density lipoprotein cholesterol levels, smoking, hypertriglyceridemia and have greater impact in women than in men [8]. In general, diabetes increases risk of CHD by 2-3 folds [10]. However, the risk for CHD is increased by 3-7 folds in diabetic women particularly [43, 62], thus eliminating the premenopausal advantage over men of the same age [52, 53, 54]. Use of high dose oral contraceptives, polycystic ovary syndrome, etc, are some of the factors affecting women only.

ADDITIONAL MATERIAL

Table 1: Additional Important Variables for Considerations.

| Variables | Quote | Reference |
|---------------------------|---|------------------------------------|
| Race/ Ethnicity | “prevalence and morbidity associated with HF are increasing in the United States, with racial and ethnic disparities” | (Ayanian & Epstein, 1991) |
| Lack of Physical Activity | “Several studies have confirmed the overall benefit of physical activity in reducing the risk of CHD” | (Sesso, Paffenbarger, & Lee, 2000) |

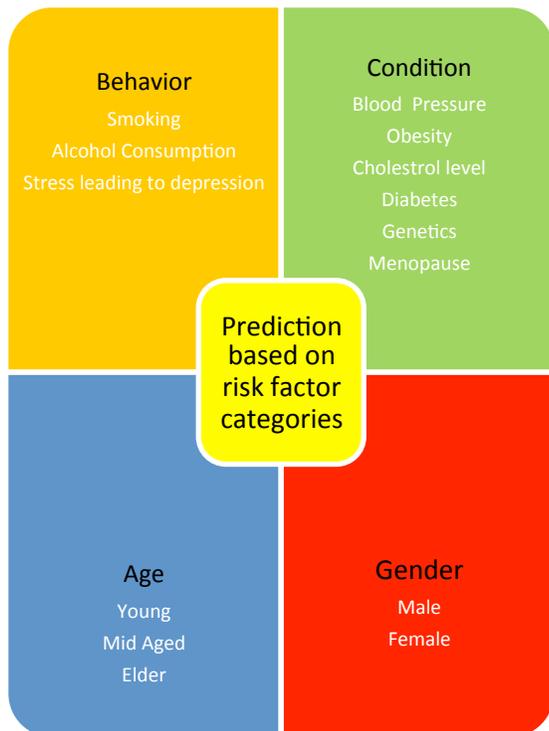
Other than the major factors categorized as risk factors for CHD ethnicity and lack of physical activity are important risk

factors to be taken into consideration on which studies has been done and are still ongoing.

Covering such a vast topic like CHD needs a lot of journal and paper analysis. Many other papers were reviewed for references for the variables discussed above which are listed in Table-2.

Table 2: Additional References for the Variables of the Model.

| Variables | References |
|----------------------|--|
| Cholesterol level | (Grundy et al., 1993) |
| High Blood Pressure | (Chobanian et al., 2003) |
| Overall Risk Factors | (Peter WF Wilson et al., 1998) |
| Obesity | (PETER W WILSON, McGEE, & KANNEL, 1981) |
| Gender | (Klag et al., 1993) |
| Diabetes | (Reaven, 1988) |
| Genetics | (Tikkanen, Havulinna, Palotie, Salomaa, & Ripatti, 2013) |
| Menopause | (Mendelsohn & Karas, 1994) |
| Diabetes | (Caprio, Wong, Alberti, & King, 1997) |
| Atherosclerosis | (Gofman, Young, & Tandy, 1966) |



Model: Risk Factor Categories in prediction of CHD

EXPLANATION/DISCUSSION OF MODEL

In this study, the various factors responsible for initiating or increasing the Cardio-vascular conditions, specifically Coronary Heart Disease (CHD), were categorized into four possible categories which are the independent variables for determining the goal or the dependent variable. The four independent variables are as follows:

- Behavior divided into Smoking, Alcohol consumption and Stress related to depression.
- Condition divided into Obesity, Blood pressure, Cholesterol level, Diabetes, Genetics and Menopause in women.
- Age as a factor was divided into three different age groups i.e. Young, Mid-aged and Elder people.
- Gender was taken as the last factor affecting CHD.

Gender and age are immutable risk factors whereas the others are modifiable.

In 1932, Wilhem Raab was able to successfully link diet with CHD in different regions ^[11]. Soon several epidemiological studies were set in motion and, in 1948, the Framingham Heart Study was initiated by the USA Public Health Service ^[12]. In 1953, the Framingham Heart Study was successfully able to identify high cholesterol and high blood pressure as important factors in the development of CHD in several populations, thus, paved the way for further research in the search of CHD risk factors ^[13]. Findings confirmed that low-density lipoprotein cholesterol (LDL-C) levels, the principal lipoprotein transporting cholesterol in blood, in young adulthood predict development of CHD later in life ^[14, 15]. This encouraged the idea that the relationship between LDL-C levels and CHD is a continuous process beginning from early adulthood ^[14, 15]. Soon, cigarette smoking was identified in the Albany Cardiovascular Health Center Study as a causative risk factor for CHD development due to high incidences of myocardial infarction and HF among smokers ^[16]. Diabetes mellitus would be quickly added to the list as it is associated with higher probability of patients presenting symptoms of hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) levels and high blood pressure ^[17]. Eventually, the Framingham Risk Score (FRS) was formulated, a multivariate statistical model that uses age, sex, blood pressure, cholesterol, smoking history and history of diabetes to estimate coronary event risk among individuals without previously diagnosed CHD ^[18]. Though risk stratification is highly recommended ^[19, 20, 21], prediction models based on CHD, including FRS have quite a few limitations in their ability to properly distinguish individuals who will develop CHD ^[18, 22]. Obesity has yet been included in standard risk assessment systems such as FRS, though it significantly contributes premature mortality from various causes of death including CHD ^[23]. This is because of major imperfections in measuring obesity ^[23]. A multi-center study in Sweden identified psychological stress as a potential factor for developing CHD due to the high incidences of ischemic stroke among spousal care givers of cancer patients, particularly among caregivers of high-mortality rate cancer patients such as lung cancer ^[24]. Eaton and colleagues demonstrated the

impact of ethnicity (along with relation to demographic factors) by proving that African-American and Caucasian post-menopausal women showed higher age-adjusted incidence of HF compared to Asians and Hispanics^[25].

The goal of the model was to predict CHD through the various independent variables. It is scientifically proven through many researches in the past that the factors chosen as the independent variables undoubtedly lead to CHD so, with the help of this model we can get all the different factors accumulated in one structure. This eventually helps us to understand their relationship with the disease and how they can be manipulated or controlled or how they will help us to get a better control over CHD at an earlier age.

INSIGHT/RECOMMENDATIONS

Risk-assessment programs like the FRS clearly show the additive nature of risk factors in CHD. However, the current FRS system should be updated with the inclusion of central obesity (using WC and WHR as measures) and psychological stress. Updating the current FRS will help estimate both relative and absolute risk associated with the various risk factors. A multifactorial approach is essential in predicting CHD event, accomplishing both primary prevention and secondary prevention, i.e. preventing and reducing mortality in CHD affected individuals. Given the numbers associated with CHD mortality^[1], intervention from the USA government and private healthcare institutions is necessary to properly combat CHD prevalence. A shining example of this is Australia. A study conducted by Clarke and Hayes showed that interventions from the Australian government and healthcare authorities have led to significant reduction in the prevalence of most of the risk factors which has led to a staggering decrease in CHD related deaths in Australia.^[64] Socioeconomic status remained a governing factor throughout the study, i.e. people with lower income had greater incidences of CHD events^[63]. Variations in event outcomes, particularly due to age-group, diabetes, gender and ethnicity suggests that the interventions require a more integrated approach. People should be encouraged to endorse physical activity instead of a sedentary lifestyle, allowing a simple, economic means of controlling the several risk factors. This can be ensured by conducting fitness or health programs at local educational and healthcare institutions, thus, covering a majority of the different age-groups. Consumption of alcohol remains a controversial issue due to the addictive and abusive problems associated. Free counseling should be provided to traumatized patients (undiagnosed of CHD) or their caregivers to help them evaluate their chances of developing CHD. Genomic epidemiological studies^[65] and risk evaluation may provide a more prospective accurate means of predicting CHD, but, the financial availability remains in doubt.

RESULTS/CONCLUSION

Analyses of data from several studies such as the Strong Heart Study, Framingham Study, etc conclude that both CHD morbidity and mortality can be controlled and significantly reduced by thorough examination of all the above mentioned risk factors. All the results cumulatively verify our hypothesis that accurate prediction, hence, primary prevention of CHD in undiagnosed individuals is possible through intensive risk factor evaluation. The inclusion novel risk factors like obesity in current risk-assessment programs like FRS are absolutely necessary as they have been proved to be univariate indicators of CHD. Further research is required to verify and later implement the genetic risk score for predicting CHD, as conducted by Tikkanen and colleagues. Diabetic patients, due to the various co-morbidities associated with the disease, should be given greater priority, particularly middle-aged diabetic women.

In light of all of the above facts and the uncertainties related to the FRS and other clinical assessment systems, it is essential to implement new strategies in order to discriminate individuals who would benefit from an early prevention intervention^[20, 26]. An initial approach would be to include the newly discovered criteria into current assessment programs, thereby, improving the prediction outcome of developing CHD. Intervention from both Government and Non-government organizations is necessary to properly combat the current cardiac crisis.

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