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Is Number of Pregnancies a Risk Factor for Heart Attack in Women?

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Is Number of Pregnancies a Risk Factor for Heart Attack in women?

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PMCH 691 - MPH Research Project

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Virginia Commonwealth University
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School of Medicine

DEPARTMENT OF PREVENTIVE MEDICINE AND COMMUNITY HEALTH

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DEDICATION

I would like to dedicate this work to my dad, Irukulla Madan Mohan, my mom, Irukulla Madhavi, and my brothers, Irukulla Naveen Kumar and Irukulla Klayan Kumar, for their innumerable patience and constant support.
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I would also like to thank Dr. Saba Masho for her patience and Lisa Anderson, Ms. Karen Bryant and Rhonda Stanfield for their support through the preparation of this project.
Is Number of Pregnancies a Risk Factor for Heart Attack in Women?

ABSTRACT:

Background: Studies regarding number of pregnancies and coronary heart disease have shown inconsistent results. In the present study, we assessed the association between number of pregnancies and heart attack (HA) in women.

Methods: Using data from NHANES III a cross sectional data analysis of 10634 women aged 17 and above was conducted. We considered socio-demographic factors and other potential risk factors including physical activity, smoking, alcohol, diabetes, hypertension, hypercholesterolemia, BMI, age, and family history of heart attack. We conducted Bivariate analysis to determine prevalence and crude odds ratios. Multivariate logistic regression analysis was used to adjust for confounding variables using SPSS.

Results: The prevalence and 95% CI of HA was 3.4% (3.0% – 3.7%). The age adjusted odds ratios for 7+ pregnancies was 2.33 95% CI [1.42-3.81], but this became insignificant when a fully adjusted model was used (odds ratio, 1.68: 95% CI, 0.89 to 3.16). For those with 4 pregnancies the risk was lowest in both age adjusted and fully adjusted models confirming the well known “J” shaped non linear relationship between number of pregnancies and heart attack.

Conclusion: We found an association that was not significant between number of pregnancies and heart attack. Further studies using physician-confirmed diagnosis is needed to appropriately asses the potential relationship of gravidity and heart attack.
INTRODUCTION

The prevalence of Coronary heart disease (CHD) and Myocardial Infarction or heart attack (MI or HA) in United States are 6.4% and 3.5% respectively \(^1\). In women the prevalence of Coronary heart disease and Myocardial Infarction are 6.0% and 2.1% \(^1\). Cardiovascular disease (CVD) continues to be the leading cause of death in women over age 50 in the United States \(^2, 3, 4, 5\). The world health organization in 1990 reported that heart disease is the leading cause of death for women of all ages in the United States. This disease accounts for nearly 30% of all deaths among women \(^5\). CVD accounted for 38.5 percent of all deaths or 1 of every 2.6 deaths in the United States in 2001 \(^1\). CVD mortality was about 60 percent of “total mortality”. This means that of over 2,400,000 deaths from all causes, CVD was listed as a primary or contributing cause on about 1,408,000 death certificates \(^1\). The potential risk factors of Myocardial Infarction are Hypertension \(^6, 7, 8\), Diabetes \(^5, 8, 9, 10\), Physical inactivity \(^12, 13, 14\), Hypercholesterolemia \(^4, 5, 11\), Obesity \(^10, 15\), Family History of MI \(^15, 16\), and Smoking \(^11, 17, 18\).

Many studies were performed to determine relationship between parity/gravidity and coronary heart disease and these studies were conflicting. About 5 prospective studies \(^19, 20, 21, 22, 23\) were performed in the past of which 4 of them had positive \(^19, 20, 21, 22\) associations between gravidity or parity and Coronary Heart disease. In addition to these studies analysis from Nurses health study compared women in the median parity group (three births) with those in the highest group (five births) and with nulliparous women showed that nulliparous women had insignificant higher coronary heart disease rates than did the median group \(^24\). A prospective study performed by Gordon et al did not find any relation between parity and CHD \(^23\). Prospective study performed by Ness et al using
Framingham and NHANES I Epidemiologic Follow-up Study (NHEFS) reported that there was 70% and 90% (after adjusting for age, Systolic blood pressure, smoking history, glucose tolerance, left ventricular hypertrophy, total cholesterol, education and Body Mass Index) increased risk respectively in multigravida women (six or more pregnancies)\textsuperscript{20}. Haynes et al found that the subset of Framingham women who were parous and worked outside the home had significantly higher rates of CHD than did parous women or nulliparous women working in the home\textsuperscript{22}. A study in Britain found 25% increased risk in married parous women with 5 or more live births than in nulliparous women\textsuperscript{19}.

Many of the case-control and cross-sectional studies conducted were inconsistent. Some studies found positive\textsuperscript{25,26} associations, some no significant relations\textsuperscript{31} and some protective effects\textsuperscript{27,28,29}. In a large cross-sectional study performed by Beral, found that parous women had lower mortality from breast, ovarian, and endometrial cancer than did nulliparous women but a higher mortality from diabetes mellitus, gallbladder disease, cancer of the uterine cervix, nephritis and nephrosis, hypertension, ischemic and degenerative heart disease, cerebrovascular disease, and all causes of death\textsuperscript{25}. A population study performed by Palmer et al found an increased relative risk of CHD in women with 5 or more births and an independently increased risk for those with first birth before age 20 after adjusting for confounding\textsuperscript{26}.

A cross-sectional study performed by Lawlor et al found a positive association between parity and CHD for those with at least 2 children, and each additional child increased the age-adjusted odds of CHD by 30% (odds ratio, 1.30; 95% confidence interval, 1.17 to 1.44) for women. Adjustment for obesity and metabolic risk factors
attenuated the associations between greater number of children and CHD in both sexes, although in women, some association remains\textsuperscript{30}. In both women and men, there were “J” shaped associations between number of children and age-adjusted prevalent CHD, with the prevalence being lowest among those with 2 children\textsuperscript{30}.

Steenland et al conducted an analysis of 585,445 women from the American Cancer Society Cancer Prevention Survey II (from 1981 to 1989). After controlling for a number of cardiovascular risk factors, they found no increased trend in heart disease with increased parity\textsuperscript{31}.

The largest case-control and cross-sectional studies showed significant positive association. Conflicting findings among other studies may have resulted because age varied among studies and degree of control for potentially confounding factors varied among studies. Those studies that used women who were aged 60 or less, an age range in which few women develop heart disease therefore these studies could not find an association and studies that found positive association included cases of all ages\textsuperscript{32}.

In the present study, we the assessed association and strength of the association between number of pregnancies and heart attack after controlling for established risk factors of CHD.
METHODS

Survey

The National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) collects, analyzes, and disseminates data on the health status of U.S. residents. The National Health and Nutrition Examination Survey (NHANES) is a periodic survey conducted by NCHS. The third National Health and Nutrition Examination Survey (NHANES III) was conducted from 1988 through 1994. About 39,695 persons were selected over the six years; of those, 33,994 (86%) were interviewed in their homes. All interviewed persons were invited to mobile examination center (MEC) for a medical examination. Seventy-eight percent (30,818) of the selected persons were examined in the MEC, and an additional 493 persons were given a special, limited examination in their homes. Participants were interviewed in their homes to determine socio-demographic, medical and family history data. A standardized set of physical examinations and laboratory measurements was performed in a mobile examination center. The overall response rate for completion of the interview and physical examination was 78% in NHANES III. The data set is divided into 5 groups, 1) adults (age ≥ 17) 2) youth (age<17) 3) EXAM (physical examination conducted at MEC) 4) Laboratory data and 5) Diet 44.

Participants

Of the 33,994 interviewed subjects in the NHANES III data set, women aged 17 years or more were selected (N=10,649). For these women, medical examination data were merged from the mobile examination center and the home exam. From this merged
data file of 10,649 females, 15 were excluded because they had heart attack before their last pregnancy resulting in a sample size of 10,634.

Our independent variable was constructed from two survey questions: the first question was “Have you ever been pregnant?” and if they answered “yes” they were asked “How many times were you pregnant?” The outcome variable for this study is heart attack (MI) and participants were asked the following question “Doctor ever told you had a heart attack?” Participants who said “yes” to this question were classified as having a heart attack (MI).

**Population characteristics**

Pregnancy, BMI and alcohol history were in the exam data files of NHANES III. The rest of the variables demographic, socioeconomic, lifestyle, other risk factors of heart attack and dependent variable (heart attack) were in the adult data files of NHANES III.

Socio-demographic characteristics included age, categorized into <29, 30-39, 40-49, 50-59, 60-69, 70-79 and 80+. The main racial backgrounds identified are non Hispanic white, non Hispanic black, Mexican American and others. Socio-economic status includes, education categorized into <8yrs ‘Elementary/Middle school’, 9-12 yrs ‘High School’ and >13yrs ‘College & above’ and family income per year is categorized into <$20,000, and >20,000 per year. Lifestyle factors included smoking, alcohol and physical activity. Smoking and alcohol was dichotomized into ‘Yes’ or ‘No’. “Jog or run, bicycle, swim, aerobic exercise, dancing, gardening weights and other sports” all these activity variables were combined into Physical activity and dichotomized into ‘Yes’ or ‘No’.
Risk factors of ischemic heart disease such as diabetes, hypertension, hypercholesterolemia, obesity (body mass index) and family history of heart attack were also included. Diabetes, hypertension and hypercholesterolemia were asked if they were diagnosed previously by a physician. Only if mother or father had history of heart attack were considered in family history of heart attack. Obesity was measured using BMI as <25 normal, 25-29 overweight and >30 obese.

Number of pregnancies was categorized in 4 different ways never been pregnant, 1, 2, 3, 4, 5, 6, and 7+ and never been pregnant, 1-2, 3-4, 5-6 and 7+ pregnancies, <2, 2, 3, 4 & 5+ pregnancies and <2, 2-4 & 5+ pregnancies.

**Statistical Methods**

The objective of this study was to determine if there was any association between number of pregnancies and heart attack in women age 17 and above and to assess the magnitude of association if there was any. The socio-demographic variables (race, income and educational level) and other potential risk factors such as age, family history of heart attack, body mass index, smoking, alcohol, physical inactivity, diabetes, hypertension, and hypercholesterolemia are used as covariates in our analysis. Epi-info 6 was used to calculate prevalence and the 95% CI. Bivariate regression analysis will be performed on un-weighted data to examine possible associations among the general characteristics of the population. Statistical analysis included for both continuous and categorical variables. Our final Logistic regression Model was based on the significance of both continuous and categorized variables at p<0.05. Variables that did not show significance in the bivariate analysis, but were considered to be risk factors in literature, were included. List of
variables included in multivariate logistic regression (models 1-5) are age, race/ethnicity, education, income, exercise, smoking, alcohol, and history of diabetes, hypertension, cholesterol and family history of heart attack. In model 6 fewer variables (income, BMI, HTN, Diabetes, Hypercholesterolemia, family history of heart attack, age) were used to adjust for number of pregnancy. Age adjusted odds ratios for different categories of number of pregnancies were calculated. Various models were assessed by categorizing number of pregnancies in different ways and taking out some of the demographic variable and non-potential risk factors of heart attack to determine an association between number of pregnancies and heart attack if there was any. SPSS 11.5 was used to calculate bivariate and multivariate logistic regression.
RESULTS

The life time prevalence of heart attack was 3.4%. While 71% of the women were pregnant at least once and 14.6% said they were never pregnant. The mean age was 47.6 yrs ranging from 17 – 90 yrs (Table 1).

The distributions of heart attack and non heart attack across different variables are shown in table 1. The majority of the women were ‘non-Hispanic white’ (43.3%), ‘≤29’ age group (24.6%), ‘High School’ educated (50.6%), ‘<$20,000’ income (50.9%), ‘Normal weight ≤ 24’ BMI (34.5%) ‘Active’ activity (61.7%), ‘Yes’ Pregnancy (71.0%) and who did not have Hypertension, Diabetes, Cholesterol, Family history of heart attack, never smoked or had alcohol. It was observed that ‘non-Hispanic white’ had the highest percentage of heart attack (64.1%). The age group ’70-79’ has the highest percentage of heart attack (33.1%), Income ‘<$20,000’ (72.4%), ‘High School’ educated (49%), Diabetics (61.9%), Non-Hypertensive (51.6%), Non Hypercholesterolemia (71.7%), BMI ≥30 (38.4%), not Smoked (56.6%), Consumed Alcohol (60.9%), Pregnant at least once (86.3%), 7+ pregnancies (22.4%) among number of pregnancies categorized into 0, 1, 2, 3, 4, 5, 6 & 7+ Pregnancies, 1-2 pregnancies (28.6%) among number of pregnancies categorized into 0, 1-2, 3-4, 5-6 & 7+ Pregnancies, 5+ Pregnancies (38.6%) among number of pregnancies categorized into <2, 2, 3, 4, & 5+ Pregnancies, 5+ Pregnancies (38.6%) among number of pregnancies categorized into <2, 2-4, & 5+ Pregnancies, Inactive (56%), and No Family History of heart attack (78.2%).
Prevalence and 95% Confidence Interval (CI) are shown in table 2. The prevalence of heart attack in this sample was 3.36%. The highest prevalence of heart attack was among Non-Hispanic Whites 4.98 and 95% CI [4.37-5.65]. Among age groups ‘80+’ had highest prevalence 11.63 and 95% CI [9.75-13.81]. Low income ‘<$20,000’ had highest prevalence of 4.66 and 95% CI [4.12-5.26]. Among Educational Levels ‘Elementary/Middle School’ seem to be having the highest prevalence 5.39 and 95% CI [4.53-6.40]. As expected the prevalence among diabetics, hypertensive & hypercholesteroleemics had the highest prevalence than those who did not, 9.92 and 95% CI [8.12-12.04], 7.04 and 95% CI [6.18-8.01] and 6.85 and 95% CI [5.79-8.09] respectively. Groups with BMI 25-29 & ≥30 had highest prevalence of 3.45 and 95% CI [2.83-4.20] & 3.73 and 95% CI [3.10-4.47] respectively. Smokers had highest prevalence of 3.89 and 95% CI [3.32-4.55] but not much different from Non smokers 3.04 and 95% CI [2.65-3.49]. Among ‘No’ group of alcohol had highest prevalence of 3.57 and 95% CI [2.90-4.37]. Women with no physical activity (Inactive) had the highest prevalence of 4.91 and 95% CI [4.28-5.64]. Prevalence among women who had a family history of heart attack had the highest prevalence 4.52 and 95% CI [3.56-5.72]. The prevalence among pregnant women was 3.1 and 95% CI [2.73-3.52] where as in non pregnant women it was 1.61[1.06-2.36]. When number of pregnancies categorized into 0, 1, 2, 3, 4, 5, 6 & 7+ pregnancies, the prevalence’s seem to increase as the number of pregnancies increase and 7+ pregnancies had the highest prevalence of 6.52 and 95% CI [5.03-8.34]. When categorized into <2, 2, 3, 4 & 5+ pregnancies 5+ had the highest prevalence of 4.96 and 95% CI [4.07-6.03] and it was twice the other prevalence.
Multivariate adjusted odds ratio and unadjusted odds ratio for heart attack are shown in table 3. In this table pregnancy is dichotomized into ‘Yes’ or ‘No’. Non-Hispanic whites had no difference in risk when compared with Non-Hispanic Blacks and the other’s group had protective effect even after adjusting 0.51 and 95% CI [0.30-0.89]. For Income level lower than $20,000 had higher risk with adjusted OR of 1.42 and 95% CI [1.00-2.02]. Elementary/Middle School was not significant but High School had highest adjusted OR of 1.74 with a significant 95% CI and 95% CI [1.14-2.67]. As age was used as a continuous variable, for increase in one year there is 7% significant increased risk of HA. Diabetes, hypertension and hypercholesterolemia all had significant higher risk than who did not have these diseases even after adjustment confirming previous studies, 2.58 [1.80-3.69], 1.81 [1.31-2.49] & 1.62 [1.2-2.19] respectively. BMI was used as a continuous variable but did not show any significant adjusted ratios though unadjusted showed minimal increase in risk of 1.02[1.01-1.04]. Though the unadjusted OR’s showed a higher risk for smoking and physical inactivity and protective effect for alcohol use there was no significant risk when adjusted for all the other variables in the table. Family history of heart attack showed a significant risk for heart attack when adjusted for all other variables with OR of 1.85 and 95% CI of [1.25-2.72]. The women who were pregnant had 16% higher risk than those who were never pregnant, but this was not statistically significant 1.16 and 95% CI [0.69-1.96].

Various models were analyzed that are shown in table 4 with their multivariate adjusted odds ratio and unadjusted odds ratio. In model 1 (Fig: 1) number of pregnancies is categorized into 0, 1, 2, 3, 4, 5, 6 & 7+ pregnancies, model 2 (Fig: 2) they are categorized into 0, 1-2, 3-4, 5-6 & 7+ pregnancies. Where as in model 3 & 4 never been
pregnant and women with one pregnancy were combined and used as a reference population, in model 3 (Fig: 3) number of pregnancies is categorized into <2, 2, 3, 4 & 5+ pregnancies and in model 4 (Fig: 4) they are categorized into <2, 2-4 & 5+ pregnancies. In model 5 pregnancy status is dichotomized in to ‘Yes’ or ‘No’. In all these models the highest unadjusted OR’s with significant 95% confidence intervals were in those women who had highest number of pregnancies that is 5+ or 7+ pregnancies. In model 6 (Fig: 5) number of pregnancies were categorized similar to model 2 but model 6 was not adjusted for education, race, smoking, alcohol use and physical activity and was adjusted only for income, diabetes, HTN, Hypercholesterolemia, BMI, Family history of heart attack and age. Though we adjusted only for important risk factors there was no significant association between number of pregnancies and heart attack. In all the models the risk was attenuated when fully adjusted but both the adjusted and unadjusted OR are in the same direction that is increasing risk with increasing number of pregnancies after 4th pregnancy. We also observed in all the models the ‘J’ shaped curve confirming previous studies. The ‘J’ curve is due to decrease in risk initially till 4th pregnancy and then starts to rise again after 4th pregnancy.

Multivariate adjusted odds ratio and unadjusted odds ratio are represented in graphical form with number of pregnancies on x-axis and odds ratios on y-axis (Fig: 1, 2, 3, 4 & 5). When fully adjusted multivariate adjusted odds ratio was attenuated when compared with unadjusted odds ratio but there was a trend of increasing risk with increasing number of pregnancies after 4th pregnancy in both multivariate adjusted odds ratio and unadjusted odds ratio. The lowest risk was observed for 4th pregnancy and thus
confirming the “J” shaped curve from previous studies. In all these models the findings were similar the only difference was categorization of number of pregnancies.

For comparison age adjusted odds ratio and multivariate adjusted odds ratio for heart attack are shown in table 5. In both Model 1 & 2 age adjusted OR had significant risk for 7+ pregnancies of 2.33 and 95% CI [1.42-3.81] and in model 3 & 4 5+ pregnancies had highest age adjusted OR 1.58 and 95% CI [1.12-2.21]. In Model 5 where pregnancy is dichotomized into ‘Yes’ or ‘No’ and the risk for pregnant women was higher than women who were never pregnant when only age was adjusted but this was not significant, odds ratio 1.52 and 95% CI [0.99-2.34].
DISCUSSION

The greater the number of pregnancies the stronger the association with heart attacks, but this was not significant. Age adjusted odds ratio for 7+ pregnancies were significantly associated with heart attack, but became insignificant when it was fully adjusted to all other risk factors. The 2 studies performed by Ness et al using Framingham data and National Epidemiologic Follow-up Study (NHEFS) data found an association with between 6+ pregnancies and CHD \(^20\). Because these studies were prospective studies this cross-sectional approach to the study may be the reason for lack of a significant association. This study considered family history of heart attack, alcohol history and physical activity where as the study performed by Ness et al did not consider these factors. This study only considered myocardial infarction as the end point or outcome variable but Ness et al study took angina pectoris, unrecognized myocardial infarction and coronary death or sudden death along with myocardial infarction. This study could not consider angina pectoris because the question asked was not reliable “did you ever have chest discomfort?” or “did you ever have chest pain?” Discomfort and chest pain could be due to various chest pathology or gastrointestinal pathology.

Lawlor et al found that number of children was inversely associated with high-density lipoprotein cholesterol and was positively associated with triglycerides and diabetes \(^30\). This study states that the risk was lowest among those with 2 children and increasing linearly with each additional child beyond 2 and for those with at least 2 children, each additional child increased the age-adjusted odds of CHD by 30% (odds ratio, 1.30; 95% confidence interval, 1.17 to 1.44) for women \(^30\). The study design used
by Lawlor et al was a cross-sectional study design but the data was obtained from a prospective data collection.

A population study performed by Beral concluded that parous women had lower mortality from breast, ovarian, and endometrial cancer than did nulliparous women but a higher mortality from diabetes mellitus, gallbladder disease, cancer of the uterine cervix, nephritis and nephrosis, hypertension, ischemic and degenerative heart disease, cerebrovascular disease, and all causes of death \(^{25}\). Though the study found a lower mortality from cancers in parous women it also found a higher mortality from other chronic disease like ischemic heart disease, diabetes and hypertension.

Prospective study performed by Colditz found an inverse relationship between parity and coronary heart disease. The discrepancy of this study is due to its small sample size and short range of age in the population \(^{24}\).

A case-control study performed by Beard et al found a relative risk of 1.9 for women whose age at first pregnancy was less than 20 and 1.8 for those whose age at first pregnancy was 20-24, as compared with those never pregnant \(^{33}\). Another hospital based case-control study performed by La Vecchia did not show any clear trend in risk with the number of live births, miscarriages, or induced abortions but showed an association in women whose first pregnancy or live birth occurred before age 20 years when compared with non pregnant women \(^{34}\). Since we did not consider age of first pregnancy in our study we cannot compare our study with these studies.

The largest case-control and cross-sectional studies showed significant positive association. Conflicting findings among other studies may have resulted because age varied among studies and degree of control for potentially confounding factors varied.
among studies. Those studies that used women who were aged 60 or less, an age range in which few women develop heart disease therefore these studies could not find an association and studies that found positive association included cases of all ages. Though our sample was large and we included all women age 17 and above the associations in this study were found not significant.

Though our study found not statistically significant association, other studies found an association. The explanations for the association are as follows (Figure 6). 1) Number of pregnancy may be associated with HA possibly because of elevation glucose levels and lipid levels. 2) Pregnancy causes physiologic anemia, nocturnal hypoventilation and circulatory overload, these could cause increased stress on heart and repeated stress in successive pregnancies can lead to increased risk of HA. 3) The hemodynamic changes and increase in progesterone levels of pregnancy appear to be the cause of arterial alterations which may lead to aneurysm formation. Aneurysms in coronary increase the risk of plaque formation and thus increase the risk for myocardial infarction.

**Conclusion**

This study determined the association between number of pregnancies and heart attack that was not significant. In our study 7+ pregnancies had insignificantly higher risk than those who were never pregnant. Further studies using physician-confirmed diagnosis is needed to appropriately assess the potential relationship of gravidity and heart attack.
TABLES
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‡ Adjusted for income, education, race, activity, smoking, alcohol BMI, HTN, diabetes, hypercholesterolemia, family history of heart attack, age.

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<td>1988</td>
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<td>[1.42-3.81]</td>
<td>877</td>
<td>1.45 [0.79-2.68]</td>
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† Adjusted for income, education, race, activity, smoking, alcohol BMI, HTN, diabetes, hypercholesterol, family history of heart attack, age.

*Adjusted for income, BMI, HTN, Diabetes, Hypercholesterolemia, Family History of Heart Attack, age.
FIGURES
Figure 1. Adjusted for income, education, race, Activity, smoking, alcohol BMI, Family History of heart attack, age, Hypertension, Diabetes, Hyper cholesterol.

![Model 1](image)

Y  UnAdj OR  Multi Variate OR

Figure 2. Adjusted for income, education, race, Activity, smoking, alcohol BMI, Family History of heart attack, age, Hypertension, Diabetes, Hyper cholesterol.

![Model 2](image)

Y  UnAdj OR  Multi Variate OR
Figure 3. Adjusted for income, education, race, Activity, smoking, alcohol BMI, Family History of heart attack, age, Hypertension, Diabetes, Hyper cholesterol.

Figure 4. Adjusted for income, education, race, Activity, smoking, alcohol BMI, Family History of heart attack, age, Hypertension, Diabetes, Hyper cholesterol.
Figure 5. Adjusted for income, BMI, Hypertension, Diabetes, Hyper cholesterol, Family History of heart attack and age.

Figure 6. How does pregnancy increase risk of HA?
REFERENCE


10. Jensen G, Nyboe J, Appleyard M, Schnohr P. Risk factors for acute myocardial infarction in Copenhagen, II: Smoking, alcohol intake, physical activity, obesity,


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