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OVARIAN DYSFUNCTION AND YOUNG WOMEN WITH ACUTE MYOCARDIAL ISCHEMIA

By

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Master of Public Health

Epidemiology

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OVARIAN DYSFUNCTION AND YOUNG WOMEN WITH ACUTE MYOCARDIAL ISCHEMIA

By

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Bachelor of Arts
Washington University in St. Louis
2008

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ABSTRACT

Background: The burden of cardiovascular disease is significant in women and men; however, the clinical presentation, risk factors, and outcomes vary. Whether the pathophysiology of ischemic heart disease has unique aspects in women and whether there are risk factors that are specific for women, such as reproductive factors, is unclear. The literature is conflicting on whether early natural menopause is associated with premature coronary heart disease in women. We hypothesize that young women who have suffered an acute myocardial infarction have more often undergone premature menopause than age-matched community-control women, and that early menopause correlates with depression.

Methods: This is a case control study comparing age and type of menopause between women who have suffered an early acute myocardial infarction (prior to the age of 60) and age and race matched controls. Cases include 49 women hospitalized at an Emory-affiliated hospital enrolled in the ongoing MI and Mental Stress (MIMS) study. Community controls were drawn from the Meta-Health study, which drew women from the Atlanta metropolitan area. Controls were matched by age (+/- 3 years) and race in a 2:1 ratio of controls to cases.

Results: The case control study population was composed of a total 147 women (49 cases and 98 controls) with mean age being 50 years old and 67.4% blacks. Cases were more likely to be current smokers (58.3% vs. 17.4%), have a history of hypertension (71.4% vs. 35.7%), a history of diabetes (20.4% vs. 7.1%), and a history of dyslipidemia (73.5% vs. 36.7%). Cases also had a higher mean BDI score (13.1 vs. 9.2). While 62.5% of cases and only 51.6% of controls had reported having undergone menopause the difference between the two groups was not statistically significant (p= 0.212). Menopausal status was not significantly associated with early acute MI in bivariate analysis.

Conclusion: Neither menopausal status nor age underwent menopause were significantly associated with early acute MI in bivariate or multivariable models. However, we found that smoking, history of dyslipidemia, and history of hypertension were significant, independent risk factors associated with high risk for early acute MI.

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Introduction

Menopause is a period in women's reproductive lifespan marked by cessation of menstrual cycling and decreased endogenous estrogen levels. Medical literature commonly associates the onset of menopause with increased coronary heart disease (CHD) secondary to estrogen deficiency; however, this relationship has been debated for decades. If menopause triggers an increased risk of CHD in women then one would expect to see an increased acceleration in the risk of CHD around the age of menopause in women. Yet, no acceleration has been noted in various epidemiological studies [1, 2]. This lack of association turns our attention to more closely examine the relationship between estrogen levels, menopause, and cardiovascular disease in women.

Estrogen and the Cardiovascular System

Estrogen is produced by the ovaries in the form of 17β-estradiol, and exerts its physiological effects through the activation of alpha and beta estrogen receptors (ERs) found throughout the body. ERs on endothelial and myocardial cells mediate a number of actions that affect the cardiovascular system. Studies in women examining exogenous estrogen administration in the form of hormonal oral contraceptives (OCPs) have shown estrogen effects on blood pressure, blood coagulability, lipoprotein profiles, glucose tolerance, and cardiac arrhythmias [3]. Animal studies have revealed that exogenous estrogen administration has anti-atherogenic properties through production of nitric oxide and alteration of gene expression [4]. These changes protect against vascular injury.

Estrogen levels vary through a woman's life and menstrual cycle regulated by the positive and negative feedback mechanisms of the hypothalamic-pituitary-axis (HPA).

The highest concentration of estrogen occurs just prior to ovulation. As women age they experience a gradual decline in ovarian function leading to menopause. The median age of natural menopause in the developed world is 51.4 [5].

The Epidemiology of Cardiovascular Disease in Women

The medical literature suggests that this transition into menopause marks the end of the cardioprotective effects of estrogen leading to increased cardiovascular disease in post-menopausal women; however, epidemiologic studies have not supported this hypothesis. A longitudinal study comparing logarithmic mortality rates in three different British cohorts showed that CHD mortality steadily increased with age with no significant peak in post-menopausal women. In contrast, a dip in the rate of mortality from breast cancer was observed in these cohorts, confirming the well-established association between endogenous estrogen and breast cancer [1]. Unlike the null findings in women undergoing natural menopause at the expected age, studies have found that women undergoing early (surgical or natural) menopause and women with pre-menopausal ovarian irregularities are at increased risk for CHD [6-12].

Premenopausal Ovarian Function and Cardiovascular Disease

It has been hypothesized that premenopausal disruptions in ovarian function escalate women's risk of developing CHD. This hypothesis has been coined the "precocious acceleration" hypothesis [13]. A prospective study following 177 menstruating female monkeys provides evidence for this theory. The study consisted of a 26-month premenopausal phase where all monkeys were divided into small groups and

fed a plaque-inducing diet. Half of the monkeys were treated with OCPs to test the hypothesis that such exposure is protective against atherosclerotic disease. In the second phase, the post-menopausal phase, all monkeys were ovariectomized. Monkeys remained in the same small groups, were fed a plaque-inducing diet, and some were given HRT. The post-menopausal phase lasted 36 months and at the end plaque-burden was assessed in the iliac and coronary arteries. Socially inferior monkeys not receiving OCPs displayed a greater degree of coronary artery atherosclerosis at the end of the study than the socially dominant, untreated peers and the socially subordinate, OCP treated peers. Post-menopausal HRT exposure did not affect the differences in atherosclerosis between the groups [14].

These findings lend nonhuman primate evidence for the "precocious acceleration" hypothesis with the implication that the premenopausal period may play a large role in understanding risk prediction and prevention for ischemic heart disease seen in peri- and post-menopausal women. It additionally suggests the importance of emotional and behavioral factors in affecting ovarian function and atherosclerosis. We have less robust evidence of this theory in human populations, partially because premenopausal ovarian dysfunction is not easily studied, as it is often subclinical.

It is common for premenopausal women to experience irregularities in their menstrual cycle. Such irregularities range from subclinical anovulatory cycles to full-blown amenorrhea. Common etiologies of premenopausal irregularities in cyclic ovarian function can be subdivided into two physiologic states: an elevated androgen state, resulting from polycystic ovary syndrome (PCOS), or a low estrogen state, referred to as functional hypothalamic amenorrhea (FHA). Elevated androgen levels, insulin

insensitivity, obesity, endothelial dysfunction, and other metabolic changes characterize PCOS [15]. FHA occurs secondary to a triad of stressors including: excessive exercise, low calorie intake, and psychological stress. Not only has psychosocial stress been associated with disruptions in ovarian function as seen in FHA, but also depression has been associated with earlier peri-menopausal transition [16]. These findings have been attributed to alterations in the HPA system.

The often sub-clinical nature of these irregularities makes it difficult to estimate and study the extent to which women experience these disturbances. However approximately 10% of women experience infertility during their reproductive years suggesting some degree of ovarian disturbance [17]. A small study that followed a cohort of 66 menstruating women for 12 months found that nearly 30% of the women's cycles showed some degree of luteal phase deficiency or to be anovulatory despite having clinically normal menstrual cycles [18].

The burden of cardiovascular disease is significant in women. Whether the pathophysiology of ischemic heart disease has unique aspects in women and whether there are risk factors that are specific for women, such as reproductive factors, remains unclear.

Study Aims

In this study we aim to further explore the association between cardiovascular disease, menopause, and emotional distress. Consistent with the "precocious acceleration" theory, we hypothesize that women who have suffered an early acute myocardial infarction, prior to age 60 years, are more likely to have undergone

menopause earlier than age-matched community-controls. Additionally we predict that post-menopausal status at younger ages correlates with the presence of depression.

Methods

Study Design and Study Population

The Emory University institutional review board approved this case control study designed to assess for association between women who have suffered early myocardial infarction (MI), defined as MI before the age of 60 and menopausal status. Cases were obtained from the MI and Mental Stress (MIMS) study database. Research personnel examined both cases and controls during a clinic visit and demographic factors and coronary heart disease risk factors were assessed with similar procedures and questionnaires. MIMs study participants included men and women ages 18-59 that were hospitalized at an Emory-affiliated hospital for acute-MI within 6 months of the study enrollment. Only the 49 women from the study were used in this analysis. (See Appendix A for MIMS study inclusion/exclusion criteria.) Controls were selected from a pool of community controls from the META-Health study, a community-based sample in the Atlanta metropolitan area. META-Health study participants had a negative cardiovascular disease history. (See Appendix B for META-Health study inclusion/exclusion criteria.) META health participants with missing data for menopausal status, BDI score, and smoking status were excluded from the pool that study controls were drawn from. After excluding those with missing data there remained a pool of 265 females from the original 317 females in the META health database. Cases and controls were randomly matched using 2-to-1 control-to-case matching on variables race (black or white) and age (+/- 3 years).

Study Variables

Data from the two studies concerning reproductive history (menopausal status, type of menopause, etc.) and depressive symptoms (Beck Depression Inventory) were collected with similar instruments. The primary variable of interest, a dichotomous variable indicating whether or not women had undergone menopause, was self-reported. If women had reported the type of menopause they underwent, yet did not report whether or not they had gone through menopause the assumption that they were post-menopausal was made. Additionally, women who did not answer whether or not they were menopausal but reported their last period was within the last 2 years were recorded as not menopausal.

Smokers were defined as current, past, or never smokers. Obesity was defined as current BMI ≥ 30. Beck Depression Inventory (BDI) was used to identify patients with depressive symptoms and was examined categorically as minimal (BDI score ≤ 13), mild (14-19), moderate (20-28), and severe (29-63). It was also reported dichotomously as depressed or not (BDI score ≥ 14). Other covariates pertaining to participants' past medical histories were collected through self-reported instruments including: history of hypertension, history of diabetes, history of dyslipidemia, and reproductive history. Measured covariates during the clinic visit include: BMI, waist circumference, lipoprotein panels, and blood pressure measurements. Demographic variables included participants' highest level of education attained, current employment status, and marital status.

Data Analysis

Means and standard deviations were reported for all continuous variables and differences between cases and controls were compared using t-tests. Pooled t-test p-values were reported when variances between cases and controls was equal. Otherwise Satterhwaite p-values were reported. The absolute number of participants and prevalence was reported for all categorical variables and comparisons between cases and controls were assessed using chi-square tests. For ordinal variables the Cochran-Mantel Haenszel statistic was used to assess differences between cases and controls. A two-sided alpha of 0.05 was used as the cutoff of for statistical significance.

To examine the relationship between menopausal status, emotional stress, and early acute MI (case status), bivariate and multivariable logistic regression analyses were performed. Odds ratios and confidence intervals of having had an early acute MI (case status) were calculated. The first multivariable model included traditional risk factors for MI, including BMI, smoking status, history of hypertension, history of diabetes, and history of dyslipidemia. In the second multivariable model, the covariate BDI score, as a measure of emotional distress, was added as a dichotomous variable. The covariate of interest, menopause status, was added to each of the above models, thus obtaining the third and fourth multivariable models. To assess the hypothesis that women with acute MIs are more likely to have undergone earlier menopause the analysis was repeated in women 55 years old and younger as well as in women 50 years old and younger.

To examine the relationship between menopausal status and depression additional bivariate and multivariable logistic regression analyses were performed. Odds ratios and confidence intervals of being menopausal were calculated. Variables identified in

previous studies to influence the age of menopause were analyzed [5, 19]. These variables included: history of heart disease (acute MI, hypertension, dyslipidemia), smoking, marital status, and highest level of education obtained. Variables significant in bivariate regression were also included in multivariable models along with the variable of interest, BDI score. To assess the effect of age, the analysis was repeated in women 55 years old and younger as well as in women 50 years old and younger.

Various interaction terms were tested to determine if there were interactions between risk factors. No interaction terms were significant and thus they were not included in the final models. Collinearity was checked using variance inflation factor (VIF) calculations and considered present if VIF was >10. Area under receiver operating characteristics (AUROC) curves assessed model discriminatory ability.

Analyses were performed using SAS software version 9.3.

Results

Study Population

The case control study population, composed of a total 147 women (49 cases and 98 controls), was matched on race and age with mean age being 50 years old and 67.4% blacks (**Table 1**). The difference between menopausal status among cases and controls was not significant with 62.5% of cases reporting being menopausal and 51.6% of controls (p= 0.212). BDI scores were higher among cases than among controls (p= 0.004). Demographically controls were more likely to have obtained a higher level of education than cases (p <0.0001). With respect to past medical history, history of dyslipidemia, history of hypertension, and current smoking, were more common in cases than in controls (p <0.0001). The mean HDL measurement in cases was 50.5 while in controls it was 62.5 (p <0.0001). Compared to the control group, cases were more likely to be current smokers (58.3% of cases versus 17.4% of controls). Cases also had a higher mean systolic blood pressure at 133.9 compared to the control mean systolic blood pressure of 122.9 (p = 0.001). Diastolic blood pressure was not significantly different between cases and controls. History of diabetes was significantly more likely among cases than controls (p = 0.018).

Bivariate Analysis

The odds of acute MI among women who reached menopause was 1.57 times that of women who had not reached menopause yet this finding was not significant (p = 0.21, **Table 2**). The odds of acute MI among depressed women was 2.84 times greater those not depressed as measured by BDI score (p= 0.005). Bivariate logistic regression confirmed that history of dyslipidemia, history of hypertension, and current smoking

status had the strongest relationship with early acute MI ($p < 0.0001$). Current smoking significantly increased odds of acute MI almost sevenfold (OR = 6.67, 95% CI: 3.07 – 14.50). Highest level of education obtained was also significant in bivariate analysis, with cases being less likely than controls to have achieved a level higher than high school ($p = 0.0002$).

Multivariable Analysis

Adjusted odds ratio estimates, 95% confidence intervals, and area under the receiver-operating curve were presented for the various multivariable models (**Table 3**). Menopausal status was not significant in any of the models. Excluding women who had used HRT at any time did not substantially change the associations between menopausal status and acute MI. The only significant risk factors associated with acute MI in all multivariable models were history of hypertension, history of dyslipidemia, and current smoking status. Smoking was most strongly correlated with early acute MI with an odds ratio of approximately 7 in all models.

***Sub-analysis of Women* ≤ 55 years and ≤ 50 years old**

Eliminating women > 55 years of age reduced the number of cases to 38 and controls to 78. In the sub-analysis of women ≤ 50 there remained only 28 cases and 50 controls. The differences between menopausal status among cases and controls remained similar and not statistically significant in sub-analysis of women ≤ 55 years and ≤ 50 years old ($p = 0.241$ and $p = 0.302$, **Tables 4 and 6**). Adjusted odds ratios for acute MI in menopausal women were also not significant in all multivariable models in the two sub-groups (**Tables 5 and 7**). The difference in presence of depression among cases

and controls remained significant in women ≤ 55 years (p= 0.032), but was not significant in women ≤ 50 (p= 0.078). In women ≤ 55 years the unadjusted odds ratio for early acute MI among depressed versus not depressed was 2.41 (95% CI 1.07-5.43). This association was lost in multivariable analysis. History of hypertension and current smoking were the two covariates that remained significantly associated with early acute MI in bivariate and multivariate models.

Depression and Menopause

A significant relationship was not seen between depression and menopausal status in either bivariate or multivariable analysis (**Table 8**). The relationship remained not statistically significant when looking at the subgroups containing only women ≤ 55 years and ≤ 50 years old. Diagnosis of hypertension and diagnosis of dyslipidemia were significant in bivariate analysis; however, only a history of hypertension remained significant when adjusting for other confounders.

Discussion

The study hypothesis that women who have early acute MI have more often undergone early menopause was not confirmed in this study population. This study found that a greater percentage of cases than controls had undergone menopause; however, the difference was not statistically significant. Menopausal status was not significantly associated with early acute MI in either bivariate or multivariable analyses. Additionally, sub-analysis of women ≤ 55 years and ≤ 50 years did not differ from these null findings. Additionally, the portion of menopausal women who had undergone natural menopause as opposed to surgical menopause was also not significantly different between cases and controls. The hypothesis that depression correlates with early menopause was also not supported in this analysis.

Current smoking status, history of hypertension, and history of dyslipidemia were found to be significant, independent risk factors associated with early acute MI. This is consistent with previous studies [20]. Current smoking status stood out as a highly associated risk factor for acute MI with an odds ratio of 7. Though this analysis does not include a dose-related analysis of cigarette smoking, previous studies have shown an association between increasing numbers of cigarettes smoked per day with increasing risk of CHD. The Nurse's Health Study showed the heaviest smokers were six times more likely than nonsmokers to have CHD [20]. Other well-established risk factors associated with cardiovascular disease included in this study were elevated BMI and history of diabetes. These covariates were all included in the final models, as all were significant at a p-value of <0.05 in bivariate analysis; however, in multivariable analysis the adjusted odds ratios for these covariates did not reach statistical significance.

Study Limitations

Many potential weaknesses were identified with this study design. As a case control study, associations between covariates can be identified; however, conclusions about causation cannot be made, limiting the inferences that can be drawn from study findings. The ideal study, yet more time and resource intensive, would be a prospective cohort study design. Additionally, the majority of the information collected was self-reported, introducing the possibility of recall bias.

One key weaknesses of this study was that some well-established risk factors for cardiovascular disease including parental cardiovascular disease history, alcohol use history, and physical activity level were not collected in a comparable form between cases and controls and thus not included in the analysis. Leaving these variables out of the analysis may have confounded the results. Age at menopause was also not available in the analysis because it was collected differently between cases and controls. Cases reported the estimated age they became post-menopausal, while controls reported the estimated age menopause began.

The menopausal transition takes place over a gradual period of up to a couple of years, and is part of the gradual decline in ovarian function in women; thus, treating menopause as a static event is a potential limitation. Menopause is defined as amenorrhea for a minimum of 12 months. The median age of natural menopause in the developed world is 51.4 [5]; however, the timing is affected by genetic and environmental factors. Multi-ethnic cohort studies have shown that having a diagnosis of heart disease and being a current smoker as well as a number of socioeconomic factors (unmarried, lower level of education obtained, and unemployment) were all

independently associated with earlier age at natural menopause. Smokers were found to undergo natural menopause 1-2 years earlier than non-smokers. Factors that correlated with later age of menopause included Japanese race, use of oral hormonal contraceptives, and parity [5, 19]. As well-established risk factors for CHD also accelerate the time of menopause, it is difficult to demonstrate an independent association between premature ovarian dysfunction and CHD. Furthermore, premature ovarian dysfunction is often subclinical and therefore the potential for misclassification of such disruptions is substantial.

Lastly, the outcome of interest, early acute MI, represents an extreme event of cardiovascular disease. It is possible that some controls, all of which had not experienced an acute event, did have subclinical coronary artery disease.

Conclusions

The association between early acute MI and early menopause did not show statistical significance in this study population. Depression was also not significantly related to menopausal status. These results do not rule out such associations, secondary to limitations of this study, particularly the small sample size. This analysis further confirms the relationship between several known risk factors for CHD and acute MI in women. Further study is needed to understand the role that ovarian function and emotional distress play in the determining the risk of CHD and MI in women.

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Table 1. Characteristics of Cases and Controls			
	Cases (n=49) *mean (SD), n (%)*	**Controls (n=98)** *mean (SD), n (%)*	**P-Value**
Demographics			
Age (years)	49.7 (6.0)	50.1 (6.1)	
Black	33 (67.4%)	66 (67.4%)	
Married	18 (36.7%)	43 (44.3%)*	0.380
Highest Level of Education > 12th grade	27 (55.1%)	83 (84.7%)	<.0001
Currently Employed	27 (55.1%)	63 (64.3%)	0.281
Anthropometrics			
BMI (kg/m^2)	32.4 (7.8)*	31.7 (8.3)*	0.650
Obesity (BMI > 30 kg/m^2)	24 (51.1%)*	45 (47.9%)*	0.721
Waist circumference (inches)	39.9 (6.3)	39.0 (7.4)	0.488
Medical History			
History of Hypertension	35 (71.4%)	35 (35.7%)	<.0001
Systolic Blood Pressure (mmHg)	133.9 (19.7)	122.9 (17.6)	0.001
Diastolic Blood Pressure (mmHg)	81.0 (10.7)	79.3 (10.7)	0.378
History of Diabetes	10 (20.4%)	7 (7.1%)	0.018
History of Dyslipidemia	36 (73.5%)	36 (36.7%)	<.0001
HDL (mg/dL)	50.5 (13.1)*	62.5 (18.0)**	<.0001
LDL (mg/dL)	93.8 (33.0)*	120.5 (36.4)**	<.0001
Total Cholesterol (mg/dL)	169.3 (42.4)*	202.8 (39.0)**	<.0001
Triglycerides (mg/dL)	127.2 (106.3)*	107.5 (71.3)**	0.266
Smoking Status			<.0001
Current Smoker	28 (58.3%)*	17 (17.4%)	
Former Smoker	0 (0%)	25 (25.5%)	
Never Smoker	20 (41.7%)	56 (57.1%)	
Depression (BDI score ≥ 14)	23 (47.9%)*	24 (24.5%)	0.004
Minimal (≤13)	25 (51.0%)	74 (75.5%)	
Mild (14-19)	11 (22.5%)	11 (11.2%)	
Moderate (20-28)	8 (16.3%)	7 (7.1%)	
Severe (≥29)	4 (8.16%)	6 (6.1%)	
Reproductive History			
Reached menopause	30 (62.5%)*	50 (51.6%)*	0.212
Natural menopause	17 (65.4%)*	32(66.7%)	0.868
Had menses in last 2 years	23 (47.9%)*	52 (54.2%)*	0.479
Ever used birth control	43 (89.6%)*	79 (80.6%)	0.170
Ever used HRT	5 (10.9%)*	18 (19.0%)*	0.224

BMI, body mass index; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol;

BDI, Beck Depression Inventory; HRT, hormone replacement therapy

*Missing between 1-5 observations

**Missing between 6 and 10 observations

Table 2. Bivariate Analysis				
Variable	**Odd Ratio Of MI**	**Lower 95% CL**	**Upper 95% CL**	**P-value**
Demographics				
Married	0.73	0.36	1.48	0.380
Highest Level of Education > 12th grade	0.22	0.10	0.49	0.0002
Currently Employed	0.68	0.34	1.37	0.282
Anthropometrics				
BMI (kg/m^2)	1.01	0.97	1.05	0.647
Obesity (BMI > 30 kg/m^2)	1.14	0.56	2.29	0.721
Waist circumference (inches)	1.02	0.97	1.07	0.486
Medical History				
History of Hypertension	4.50	2.14	9.48	<.0001
Systolic Blood Pressure (mmHg)	1.03	1.01	1.05	0.002
Diastolic Blood Pressure (mmHg)	1.02	0.98	1.05	0.376
History of Diabetes	3.33	1.18	9.40	0.023
History of Dyslipidemia	4.77	2.24	10.15	<.0001
HDL (mg/dL)	0.95	0.92	0.98	0.0003
LDL (mg/dL)	0.98	0.97	0.99	0.0002
Total Cholesterol (mg/dL)	0.98	0.97	0.99	<.0001
Triglycerides (mg/dL)	1.00	1.00	1.01	0.225
Current Smoker	6.67	3.07	14.50	<.0001
Depression (BDI score ≥ 14)	2.84	1.37	5.88	0.005
Reproductive History				
Reached menopause	1.57	0.77	3.18	0.213
Natural menopause	0.94	0.35	2.58	0.911
Had menses in last 2 years	0.78	0.39	1.56	0.480
Ever used birth control	2.07	0.72	5.93	0.176
Ever used HRT	0.52	0.18	1.51	0.229

MI, myocardial infarction; BMI, body mass index; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; BDI, Beck Depression Inventory; HRT, hormone replacement therapy

Table 3. Modeling Acute MI and Potential Risk Factors						
Variable	**Bivariate Analysis** OR (95% CI)	**Model 1: Traditional Risk Factors** OR (95% CI)	**Model 2: Traditional Risk Factors and Depression** OR (95% CI)	**Model 3: Traditional Risk Factors and Menopause** OR (95% CI)	**Model 4: Traditional Risk Factors with Menopause and Depression** OR (95% CI)	**Model 5: Traditional Risk Factors with Menopause and Education** OR (95% CI)
Reached menopause	1.60 (0.78 - 3.12)			0.86 (0.35-2.15)	0.92 (0.36-2.32)	0.82 (0.32-2.08)
BMI	1.01 (0.97-1.05)	0.97 (0.92-1.03)	0.97 (0.92-1.03)	0.97 (0.92-1.03)	0.97 (0.91-1.03)	0.97 (0.92-1.03)
History of Hypertension	4.50 (2.14-9.48)	4.32 (1.72 - 10.80)	4.16 (1.65-10.46)	4.40 (1.73-11.19)	4.20 (1.64-10.74)	4.48 (1.75-11.48)
History of Diabetes	3.33 (1.18-9.40)	2.96 (0.80-11.01)	3.22 (0.85-12.20)	2.95 (0.80-10.97)	3.12 (0.84-12.12)	3.06 (0.81-11.56)
History of Dyslipidemia	4.77 (2.24-10.15)	2.77 (1.14-6.72)	2.51 (1.01-6.25)	2.82 (1.14-6.96)	2.54 (1.00-6.45)	2.48 (0.98-6.23)
Current Smoker	6.67 (3.07-14.50)	7.11 (2.87-17.63)	6.81 (2.73-16.99)	7.14 (2.87-17.78)	6.80 (2.72-17.05)	6.16 (2.43-15.65)
Depression (BDI score ≥ 14)	2.84 (1.37-5.88)		1.59 (0.62-4.12)		1.57 (0.60-4.10)	
Highest Level of Education > 12th grade	0.22 (0.10-0.49)					0.43 (0.15-1.18)
AUROC		0.8430	0.8451	0.8436	0.8453	0.8541

BMI, body mass index; BDI, Beck Depression Inventory; AUROC, area under the receiver-operating characteristic curve

Table 4. Characteristics of Cases and Controls ≤ 55 years old			
	Cases (n=38) *mean (SD), n (%)*	**Controls (n=78)** *mean (SD), n (%)*	**P-Value**
Demographics			
Age (years)	47.4 (4.7)	47.8 (4.7)	
Black	28 (73.7%)	59 (74.7%)	
Married	13 (34.2%)	33 (42.3%)*	0.403
Highest Level of Education > 12th grade	23 (60.5%)	67 (85.9%)	0.002
Currently Employed	18 (47.4%)	49 (62.8%)	0.114
Anthropometrics			
BMI (kg/m^2)	32.6 (8.4)*	32.5 (8.7)*	0.958
Obesity (BMI > 30 kg/m^2)	19 (51.4%)*	39 (51.3%)*	0.721
Waist circumference (inches)	40.6 (6.4)	39.2 (7.1)	0.296
Medical History			
History of Hypertension	134.9 (20.1)	122.0 (16.2)	0.0003
Systolic Blood Pressure (mmHg)	82.1 (11.4)	79.7 (10.3)	0.276
Diastolic Blood Pressure (mmHg)	26 (68.4%)	27 (34.2%)	0.0001
History of Diabetes	8 (21.1%)	7 (8.7%)	0.065
History of Dyslipidemia	27 (71.1%)	28 (35.4%)	0.0003
HDL (mg/dL)	49.6 (13.3)*	62.1 (18.1)**	0.005
LDL (mg/dL)	94.4 (34.5)*	119.4 (37.5)**	0.002
Total Cholesterol (mg/dL)	169.2 (41.4)*	200.8 (39.9)**	0.0003
Triglycerides (mg/dL)	128.5 (110.3)*	105.8 (75.7)**	0.285
Smoking Status			<.0001
Current Smoker	23 (62.2%)*	15 (19.0%)	
Former Smoker	0 (0%)	18 (22.8%)	
Never Smoker	14 (37.8%)	46 (58.2%)	
Depression (BDI score ≥ 14)	18 (48.7%)*	22 (28.2%)	0.032
Minimal (≤13)	19 (50.0%)	56 (70.9%)	
Mild (14-19)	10 (26.3%)	11 (13.9%)	
Moderate (20-28)	4 (10.5%)	6 (7.7%)	
Severe (≥29)	4 (10.5%)	5 (6.3%)	
Reproductive History			
Reached menopause	19 (51.4%)*	31 (39.7%)*	0.241
Natural menopause	11 (68.8%)*	17 (58.6%)*	0.543
Had menses in last 2 years	23 (62.2%)*	52 (67.5%)*	0.571
Ever used birth control	33 (89.2%)*	63 (79.7%)	0.21
Ever used HRT	2 (5.7%)*	12 (15.6%)*	0.143

BMI, body mass index; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; BDI, Beck Depression Inventory; HRT, hormone replacement therapy

*Missing between 1-5 observations

**Missing between 6 and 10 observations

Table 5. Modeling Acute MI and Potential Risk Factors in Women ≤ 55 years old						
Variable	**Bivariate Analysis** OR (95% CI)	**Model 1: Traditional Risk Factors** OR (95% CI)	**Model 2: Traditional Risk Factors and Depression** OR (95% CI)	**Model 3: Traditional Risk Factors and Menopause** OR (95% CI)	**Model 4: Traditional Risk Factors with Menopause and Depression** OR (95% CI)	**Model 5: Traditional Risk Factors with Menopause and Education** OR (95% CI)
Reached menopause	1.65 (0.75-3.65)			0.91 (0.34-2.43)	0.93 (0.35-2.50)	0.92 (0.34-2.47)
BMI	1.00 (0.96-1.05)	0.96 (0.90-1.03)	0.96 (0.90-1.02)	0.96 (0.90-1.02)	0.96 (0.90-1.02)	0.96 (0.90-1.02)
History of Hypertension	4.09 (1.79-9.37)	3.58 (1.32-9.65)	3.45 (1.26-9.43)	3.59 (1.32-9.79)	3.46 (1.25-9.57)	3.53 (1.29-9.67)
History of Diabetes	2.70 (0.90-8.13)	2.32 (0.56-9.55)	2.46 (0.58-10.36)	2.33 (0.57-9.59)	2.46 (0.58-10.35)	2.27 (0.54-9.51)
History of Dyslipidemia	4.38 (1.89-10.15)	2.69 (1.02-7.13)	2.53 (0.92-6.96)	2.71 (1.01-7.28)	2.55 (0.91-7.15)	2.42 (0.88-6.66)
Current Smoker	6.90 (2.89-16.49)	5.71 (2.17-15.01)	5.58 (2.11-14.75)	5.72 (2.15-15.19)	5.58 (2.09-14.90)	5.24 (1.94-14.12)
Depression (BDI score ≥ 14)	2.41 (1.07-5.43)		1.26 (0.44-3.64)		1.25 (0.43-3.62)	
Highest Level of Education > 12th grade	0.25 (0.10-0.63)					0.56 (0.18-1.78)
AUROC		0.8293	0.8311	0.8292	0.8300	0.8307

BMI, body mass index; BDI, Beck Depression Inventory; AUROC, area under the receiver-operating characteristic curve

Table 6. Characteristics of Cases and Controls ≤ 50 years old			
	Cases (n=28) *mean (SD), n (%)*	**Controls (n=50)** *mean (SD), n (%)*	**P-Value**
Demographics			
Age	45.5 (4.1)	45.3 (3.8)	0.828
Black	22 (78.6%)	40 (80.0%)	0.881
Married	8 (28.6%)	22 (44.0%)	0.179
Highest Level of Education > 12th grade	16 (57.1%)	44 (88.0%)	0.002
Currently Employed	12 (42.9%)	34 (68%)	0.030
Anthropometrics			
BMI (kg/m^2)	33.3 (8.7)	31.3 (8.1)*	0.293
Obesity (BMI > 30 kg/m^2)	14 (50.0%)	22 (35.8%)*	0.726
Waist circumference (inches)	41.0 (6.3)	38.0 (6.4)	0.049
Medical History			
History of Hypertension	18 (64.3%)	14 (28.0%)	0.002
Systolic Blood Pressure (mmHg)	132.6 (18.2)	120.8 (16.0)	0.004
Diastolic Blood Pressure (mmHg)	82.2 (10.8)	79.3 (11.0)	0.274
History of Diabetes	6 (21.4%)	4 (8.0%)	0.089
History of Dyslipidemia	19 (67.9%)	16 (32.0%)	0.002
HDL	48.9 (13.9)*	60.8 (15.2)*	0.002
LDL	98.5 (35.8)*	117.9 (41.8)*	0.051
Total Cholesterol	171.0 (41.4)*	197.7 (44.2)*	0.014
Triglycerides	117.7 (68.5)*	103.8 (86.9)*	0.487
Smoking Status			0.001
Current Smoker	17 (63.0%)*	9 (18.0%)	
Former Smoker	0	6 (12.0%)	
Never Smoker	10 (37. 0%)	35 (70.0%)	
Depression (BDI score ≥ 14)	13 (48.2%)*	14 (28.0%)	0.078
Minimal (≤13)	14 (50%)	36 (72.0%)	
Mild (14-19)	7 (25.0%)	6 (12.0%)	
Moderate (20-28)	4 (14.3%)	4 (8.0%)	
Severe (≥29)	2 (7.1%)	4 (8.0%)	
Reproductive History			
Reached menopause	9 (33.3%)*	11 (22.5%)*	0.302
Natural Menopause	5 (55.6%)	6 (54.6%)	0.964
Had menses in last 2 years	21 (77.8%)*	42 (87.5%)*	0.270
Ever used Birth Control	26 (96.3%)*	39 (78.0%)*	0.035
Ever used HRT	1 (4.0%)*	4 (8.3%)*	0.487

BMI, body mass index; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; BDI, Beck Depression Inventory; HRT, hormone replacement therapy

*Missing between 1-5 observations

Table 7. Modeling Acute MI and Potential Risk Factors in Women ≤ 50 years old						
Variable	**Bivariate Analysis** OR (95% CI)	**Model 1: Traditional Risk Factors** OR (95% CI)	**Model 2: Traditional Risk Factors and Depression** OR (95% CI)	**Model 3: Traditional Risk Factors and Menopause** OR (95% CI)	**Model 4: Traditional Risk Factors with Menopause and Depression** OR (95% CI)	**Model 5: Traditional Risk Factors and Marital Status** OR (95% CI)
Reached menopause	1.73 (0.61-4.91)			0.90 (0.24-3.37)	0.89 (0.23-3.42)	0.87 (0.23-3.30)
BMI	1.03 (0.97-1.09)	0.98 (0.90-1.06)	0.98 (0.90-1.06)	0.98 (0.90-1.06)	0.98 (0.90-1.06)	0.97 (0.89-1.06)
History of Hypertension	4.63 (1.72-12.45)	3.18 (0.96-10.47)	3.18 (0.95-10.64)	3.12 (0.96-10.37)	3.17 (0.95-10.59)	3.01 (0.89-10.16)
History of Diabetes	3.14 (0.80-12.26)	2.75 (0.49-15.57)	2.74 (0.48-15.61)	2.77 (0.49-15.62)	2.76 (0.49-15.61)	3.34 (0.54-20.57)
History of Dyslipidemia	4.49 (1.67-12.09)	2.13 (0.65-7.00)	2.14 (0.60-7.68)	2.15 (0.64-7.24)	2.18 (0.58-8.16)	1.76 (0.50-6.17)
Current Smoker	7.74 (2.67-22.43)	4.98 (1.55-15.96)	4.99 (1.54-16.14)	4.98 (1.54-16.15)	5.01 (1.52-16.50)	4.46 (1.33-14.96)
Depression (BDI score ≥ 14)	2.39 (0.90-6.33)		0.98 (0.27-3.58)		0.96 (0.26-3.56)	
Highest Level of Education > 12th grade	0.18 (0.06-0.57)					0.29 (0.07-1.24)
AUROC		0.8248	0.8248	0.8243	0.8258	0.8345

BMI, body mass index; BDI, Beck Depression Inventory; AUROC, area under the receiver-operating characteristic curve

Table 8. Modeling Factors associated with Menopause						
	All Women (n=147)		**Women ≤ 55 years (n=116)**		**Women ≤ 50 years (n=78)**	
Variable	**Bivariate Analysis** OR (95% CI)	**Model 1: Traditional Risk Factors** OR (95% CI)	**Bivariate Analysis** OR (95% CI)	**Model 1: Traditional Risk Factors** OR (95% CI)	**Bivariate Analysis** OR (95% CI)	**Model 1: Traditional Risk Factors** OR (95% CI)
Depression (BDI score ≥ 14)	0.88 (0.44-1.79)	0.58 (0.27-1.28)	1.14 (0.52-2.46)	0.67 (0.28-1.65)	0.97 (0.33-2.82)	0.40 (0.10-1.55)
History of Acute MI (case)	1.57 (0.77-3.18)		1.65 (0.75-3.65)		1.73 (0.61-4.91)	
History of Hypertension	2.47 (1.26-4.85)	2.28 (1.12-4.67)	2.65 (1.23-5.68)	2.46 (1.09-5.53)	2.20 (0.78-6.40)	2.08 (0.67-6.50)
History of Dyslipidemia	2.17 (1.11-4.22)	2.05 (0.98-4.28)	2.32 (1.09-4.95)	2.16 (0.94-5.00)	3.10 (1.07-8.99)	4.01 (1.14-14.09)
Current Smoker	1.33 (0.65-2.72)		1.80 (0.82-3.96)		2.50 (0.87-7.15)	
BMI	1.00 (0.96-1.04)		1.02 (0.97-1.06)		1.06 (0.99-1.13)	
Married	0.76 (0.39-1.49)		0.53 (0.24-1.16)		0.44 (0.14-1.39)	
Highest Level of Education > 12th grade	0.53 (0.24-1.16)		0.63 (0.26-1.53)		0.57 (0.18-1.82)	
AUROC		0.6542		0.6623		0.7036

MI, myocardial infarction; BDI, Beck Depression Inventory; BMI, body mass index; AUROC, area under the receiver-operating characteristic curve

Appendix A

MIMS Inclusion/Exclusion Criteria

Inclusion Criteria:

- History of documented MI within the past 6 months
- Age 18-59 years old

Exclusion Criteria:

- History of unstable angina, myocardial infarction, or decompensated heart failure in the past week
- Patients deemed to be unsafe to hold anti-ischemic medications for the 48 hours prior to the testing
- Systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg on the day of the test
- Physical limitations with inability to exercise on a treadmill (Duke Activity Status Index [DASI]<5 METs)
- History of current alcohol or substance abuse or dependence (past year); or history of severe psychiatric disorder other than major depression, such as schizophrenia
- History of serious medical disorder other than cardiovascular disease that may interfere with the study results, e.g. cancer, renal failure
- Use of exogenous estrogens or progesterone (past 3 months)
- Current psychotropic medication treatment (past month) except treatment for depression
- Pregnancy
- Severe aortic stenosis

Appendix B

META-Health Inclusion/Exclusion Criteria

Inclusion Criteria:

- Race White or Black
- Age 30-65 years old
- Resident of Fulton, Dekalb, or Cobb County, Georgia
- Male or Female