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BMJ Open   Myocardial infarction in the Wisconsin Longitudinal Study: the interaction among environmental, health, social, behavioural and genetic factors

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ABSTRACT

Objectives: This study examined how environmental, health, social, behavioural and genetic factors interact to contribute to myocardial infarction (MI) risk.

Design: Survey data collected by Wisconsin Longitudinal Study (WLS), USA, from 1957 to 2011, including 235 environmental, health, social and behavioural factors, and 77 single-nucleotide polymorphisms were analysed for association with MI. To identify associations with MI we utilized recursive partitioning and random forest prior to logistic regression and chi-squared analyses.

Participants: 6198 WLS participants (2938 men; 3260 women) who (1) had a MI before 72 years and (2) had a MI between 65 and 72 years.

Results: In men, stroke (LR OR: 5.01, 95% CI 3.36 to 7.48), high cholesterol (3.29, 2.59 to 4.18), diabetes (3.24, 2.53 to 4.15) and high blood pressure (2.39, 1.92 to 2.96) were significantly associated with MI up to 72 years of age. For those with high cholesterol, the interaction of smoking and lower alcohol consumption increased prevalence from 23% to 41%, with exposure to dangerous working conditions, a factor not previously linked with MI, further increasing prevalence to 50%. Conversely, MI was reported in <2.5% of men with normal cholesterol and no history of diabetes or depression. Only stroke (4.08, 2.17 to 7.65) and diabetes (2.71, 1.81 to 4.04) by 65 remained significantly associated with MI for men after age 65. For women, diabetes (5.62, 4.08 to 7.75), high blood pressure (3.21, 2.34 to 4.39), high cholesterol (2.03, 1.38 to 3.00) and dissatisfaction with their financial situation (4.00, 1.94 to 8.27) were significantly associated with MI up to 72 years of age. Conversely, often engaging in physical activity alone (0.53, 0.32 to 0.89) or with others (0.34, 0.21 to 0.57) was associated with the largest reduction in odds of MI. Being non-diabetic with normal blood pressure and engaging in physical activity often lowered prevalence of MI to 0.2%. Only diabetes by 65 (4.25, 2.50 to 7.24) and being exposed to dangerous work conditions at 54 (2.24, 1.36 to 3.69) remained significantly associated with MI for women after age 65, while still menstruating at 54 (0.46, 0.23 to 0.91) was associated with reduced odds of MI.

Strengths and limitations of this study

- 54-year-long longitudinal survey study (Wisconsin Longitudinal Study, WLS).
- Large number of participants with high response rates.
- Large breadth of factors, including environmental, health, social, behavioural and genetic.
- Genetic data used in this study were limited due to prior selection of single-nucleotide polymorphisms by WLS.
- WLS participants are almost exclusively middle-class to upper-middle-class, non-Hispanic whites from Wisconsin, therefore social-factor homogeneities reduce generalisability.

Conclusions: Together these results indicate important differences in factors associated with MI between the sexes, that combinations of factors greatly influence the likelihood of MI, that MI-associated factors change and associations weaken after 65 years of age in both sexes, and that the limited genotypes assessed were secondary to environmental, health, social and behavioral factors.

INTRODUCTION

Heart disease impacts ~26.6 million US adults and is the leading cause of death among men and women in the USA, accounting for 25% of deaths (~600 000 people) annually.[1] [2] An estimated 935 000 people in the USA suffer from a myocardial infarction (MI) every year.[3]

MI is a symptom of advanced or severe heart disease,[4–6] and the major modifiable risk factors for MI include high blood pressure,[3 7 8] high blood cholesterol,[9–13] diabetes (mellitus),[14–16] smoking/tobacco use,[17–21] obesity and being overweight,[22–27] poor nutrition/diet,[28–36] physical inactivity[37–41] and (no or excessive) alcohol use.[42–47] Stress has also been shown to be an important (modifiable) risk

factor for MI.[48–51] The major non-modifiable risk factors for MI include sex,[52–57] age,[3 58 59] family history[60–63] and race.[1 3 64] However, not all individuals with these risk factors experience a MI. Thus, it is likely that combinations of these risk factors, or as yet unknown risk factors, are important in the aetiology of the disease.

Other non-modifiable risk factors include genetic polymorphisms such as those identified in *APOE* (apolipoprotein E)[65 66] *CETP* (cholesteryl ester transfer protein)[67–69] and *CDKN2A/2B* (cyclin-dependent kinase 2A/2B),[70] but there is no consensus about which gene (s) are most predictive of MI. In addition, there are few large-scale studies that have looked at the interactions between genetic and environmental, health, social and behavioural factors that predict MI.

Research has shown that risk factors for heart disease and MI are moderated by sex and age, and the interaction of risk factors with heart disease and MI affects men and women differently at different ages throughout their lives.[53–55 57 71] For example, women are more likely than men to die within 1 year of experiencing an MI when younger,[72 73] but in general first experience MI later in life than do men,[55] although men are more likely to experience MI overall.[3] Identification of sex-specific factors associated with MI and how those associations change over time is important for predicting disease risk throughout life.

In this study, we examined how the interaction among environmental, health, social, behavioural and genetic factors associates with MI, with the goal of determining (1) differences in factors associated with MI between men and women, with a focus on the interaction among factors; (2) how interactions among these factors affect MI occurrence; (3) how factors associated with MI change over a person's lifetime, again with a focus on the interaction among factors and (4) what combined factors are associated with reduced occurrence of MI, even in the presence of other known risk factors.

METHODS
Study participants and WLS survey data
The Wisconsin Longitudinal Study (WLS) is a 54-year-long survey study on the lives of a cohort of 1957 Wisconsin high-school graduates. The original cohort of participants was made up of 10 317 men and women, randomly selected from those graduating from a Wisconsin high school in 1957. Self-reported survey data were collected from WLS graduate participants in 1957, 1964, 1975, 1993, 2004 and 2011. Data from each of the aforementioned survey rounds were included in this study, with many of the selected variables representing the same questions asked at multiple time points (WLS survey rounds). In addition, DNA saliva samples were provided by a subset of the WLS (4562 graduates) and 77 single-nucleotide polymorphisms (SNPs) were genotyped for each of these participants in 2009, providing genetic data for a subset of the WLS as well. Additional information about the WLS survey data and participants can be found elsewhere[74 75] (http://www.ssc.wisc.edu/wlsresearch/).

The WLS has enjoyed high response rates across multiple survey waves. The data for the current analyses come primarily from the 1993, 2004, and 2011 survey waves when the cohort was 53, 64 and 71 years old, respectively. In 1993, 8493 cohort members participated in the telephone survey, 588 refused to participate, 587 were deceased and 649 were unfielded for either administrative reasons or permanent disability. In 2004, 7265 cohort members participated in the telephone survey, 956 refused, 1287 were deceased and 809 were unfielded. Finally, for the 2011 in-home interview, 5968 cohort members participated in the survey, 1088 refused, 1587 were deceased and 1674 were unfielded (see online supplementary table S1). Among those not deceased, response rates for these survey waves were 87%, 80% and 60%, respectively. Also excluding unfielded cases from the denominator brings the response rates to 94%, 88% and 85%.

Study questions and dependent variables
This study examined factors potentially associated with MI using environmental, health, social, behavioural and genetic data available through the WLS. Two sets of data were analysed based on survey years of data collection, looking at anyone who reported a MI up to 72 years of age and only those who reported a MI between 65 and 72 years. We did this for two reasons: (1) to examine MI up to 72 years and what factors would be associated with this group regardless of when their MI occurred; and (2) an analysis of factors that occurred only *before* a MI. Owing to the timing of the survey years, this allowed us to look at factors associated with MI at any point in one's lifetime (up to 72 years), versus factors associated with a MI in 'older age' (65–72 years).

In order to create our two dependent variables, we compiled data from the 2004 and 2011 WLS surveys including National Death Index (NDI) data. The first dependent variable, 'MI by 72 years of age', was coded as 'yes' if a participant reported experiencing a MI in 2004 or 2011 or died of MI according to the NDI (ICD-9 or ICD-10 codes; note: NDI data were collected by the WLS only up to 2006 at the time of the current study), thereby including anyone who reported having a MI to the WLS. The dependent variable was coded 'no' only if no previous MIs were reported and the participant reported no MIs in 2011. This resulted in MI data for 6198 graduates, with 776 participants coded as 'yes' and 5422 coded as 'no' for the given variable. Additionally, this dependent variable was linked to a data set which included independent variables from all WLS survey years, 1957–2011. Characteristics of the WLS participants included in this study population are shown in table 1. The second dependent variable, 'MI between 65 and 72 years of age', was coded similarly to the first, but included *only* those participants who reported no MIs by 2004, thereby excluding individuals who had a MI before 65 years of age. This dependent variable was coded as 'yes' if the participant reported having a MI

Table 1 Participant characteristics for those included in the current study

Characteristic, survey year collected	Total population: n (%) *or* mean (± SD)	Males: n (%) *or* mean (± SD)	Females: n (%) *or* mean (± SD)
'MI by 72 years of age' DV	6198	2938 (47.4%)	3260 (52.6%)
Included in DV 'MI Between 65 and 72'	5321 (85.9%)	2404 (81.8%)	2917 (89.5%)
Ever experienced MI	776 (12.5%)	533 (18.1%)	243 (7.5%)***
IQ Score (Henmon-Nelson), 1957	102.1 (14.77)	101.9 (15.22)	102.2 (14.37)
Years of education‡, 1993	13.75 (2.33)	14.14 (2.55)	13.41 (2.05)***
Age at interview, 2004	64.33 (0.70)	64.40 (0.73)	64.27 (0.67)***
Married, 2004	4652 (78.6%)	2368 (85.4%)	2284 (72.7%)***
Total household income, 2004	$30 619 ($7)	$42 364 ($6)	$22 961 ($8)***
Smoker, 2004	613 (11.6%)	296 (12.0%)	317 (11.2%)
Alcohol (days/month), 2004	7.57 (9.67)	9.47 (10.50)	5.89 (8.54)***

Significant differences between men and women are indicated, and based on Student's *t*-test or equal proportions test.
'***'=p<0.001.
‡Summary of equivalent years of regular education based on highest degree.
DV, dependent variable; MI, myocardial infarction; SD, standard deviation.

between 2004 and 2011 (in 2011) or died of acute MI after 2004 and was coded as 'no' if the participant reported no MIs in 2011. This resulted in MI data for 5321 graduates, with 213 participants coded as 'yes' and 5108 coded as 'no'. This dependent variable was linked to a data set which included only independent variables collected during the 2004 survey year or earlier. Information about specific WLS variables used to create the two dependent variables for the current study is provided in online supplementary information 1.

Environmental, health, social and behavioural data

From the data generated by the WLS, official release V.13.01, we analysed 235 environmental, health, social and behavioural variables against MI data for WLS participants included in this study. These included descriptive, family, spouse, children, personality, medical history, family's medical history, general health and weight, exercise, sleep, smoking, alcohol consumption, social, work-related, socioeconomic, life satisfaction, stress-related and coping, stressful life events, summary psychological and personality variables collected by the WLS (see online supplementary table S2). We analysed an additional 26 variables in all female-specific analyses, which included variables related to menstruation, menopause, reproductive surgeries and hormone replacement therapies.

One variable, 'Summary Score Anger Index, 2004', was updated by the WLS during the course of this study, in July 2014. Therefore, for this variable the updated version 13.02 data were substituted for the version 13.01 data for all analyses conducted. Additionally, in the WLS surveys there were some questions that were asked of only a subset of the WLS participants, specifically, the alcohol-related and depression-related questions were only asked of a 79% random subset of the WLS.

SNP genotyping data

Of the 4562 graduates who provided DNA saliva samples to the WLS, 4012 also answered the MI questions and were therefore included in the SNP analyses for this study. A total of 77 SNPs were genotyped for each of these participants in 2009, as described in Roetker *et al.*[76] This study also included five additional genetic variables based on APOE, because of its known association with cardiovascular and other disease states.[65 77–79] Three APOE alleles: APOE ε2, APOE ε3 and APOE ε4, determined by the SNPs rs429358 and rs7412 were used to determine APOE status.[80 81] From this, we created five variables, allele APOE4±, allele APOE2±, genotype E4/E4, genotype E2/E2 and specific APOE genotype (see online supplementary table 2).

Statistical analyses

This study looked for independent as well as interactive effects of environmental, health, social, behavioural and genetic variables for the 6198 and 5321 WLS graduates for which data were available for our two dependent variables (MI by 72 years and MI between 65 and 72), respectively. Of these, 4012 and 3684 respectively, also provided genetic data which was analysed for independent as well as interactive effects separately and in combination with environmental, health, social and behavioural data, in order to identify the combination of factors most associated with MI. In order to address possible collinearity of covariates measured in multiple survey rounds, we first completed a recursive partitioning (RP) and random forest (RF) analysis in order to reduce the number of variables analysed and then ran independent logistic regression (LR) analysis for each independent variable identified, rather than a multiple regression analysis of all independent variables. A similar strategy, using machine-learning methodologies to identify associations followed by LR analysis of individual factors, has been used in prior studies.[76]

Recursive partitioning

RP was used to create classification trees to determine main factor and interactive effects associated with MI

using environmental, health, social, behavioural and genetic variables, individually and combined, in order to assess whether MI is better explained by our environment, our genetics or a combination of both. All RP analyses were completed using the R program, V.2.15.2 (R: A language and environment for statistical computing (program), Vienna, Austria: R Foundation for Statistical Computing, 2008) with package 'rpart' (rpart: Recursive Partitioning (program), R package version 3.1-55. version, 2012), based on Breiman's classification and regression trees algorithm.[82] The usesurrogate parameter was set to 0, maxcompete was set to 0, maxsurrogate was set to 0 and the complexity parameter was set to 0.01. A 10-fold cross-validation procedure was used to determine how far back to prune the trees. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using MedCalc (http://www.medcalc.org/calc/odds_ratio.php; calculations according to Altman[83]). When zeros appeared in the terminal nodes of the RP trees, MedCalc used an ad hoc method to determine estimates of OR.[84 85]

Random forest

RF[86–89] was used in our association analyses[90–93] and was conducted using the 'randomForest' package[94] (Online R documentation for the package 'randomForest' (program), 4.6-10 version, 2014) available with the R program. We chose to use 'margin measure' or mean decrease in accuracy to determine variable importance.[95 96] Missing values were imputed for independent variables using the 'na.roughfix' command, which imputes missing values using either the median value for numeric variables, or the most frequent level for factor variables. Using imputed values with the 'rfImpute' command for missing data was considered here, but the bias that was noted in preliminary analyses was considered too great. Three trials of RF were conducted for each 'variable importance' measure, to determine the replicability of the results, in large part because of the randomness associated with this particular test. Using the dependent variable 'MI by 72 years of age' and associated data set, the 'mtry' parameter was set to 34 for men and 36 for women, based on the lowest out-of-bag (OOB) estimate of error rate of 12.25% and 5.09%, respectively. Using the dependent variable 'MI between 65 and 72 years of age' and associated data set, the 'mtry' parameter was set to 30 for men and 32 for women, based on the OOB estimate of error rate of 5.87% and 2.47%, respectively. The number of trees in the forest, the 'ntree' parameter, was set to 5000 for men and women in both analyses.

LR and χ^2

Single-factor associations with MI were determined for all environmental, health, social, behavioural and genetic variables that appeared in either the RP tree(s) or the RF list(s) of 'important' variables generated for each of the dependent variable analyses, using a LR model and χ^2 test with R. For those cases where the sample size (one or more categories) was too small for a χ^2 test (n<5), Fisher's Exact test was used to calculate significance. When necessary, Fisher's Exact test p values were obtained using Monte Carlo simulation. LR ORs were determined by exponentiating the coefficients of the regression models using the R program. All p values generated from these tests were adjusted for multiple testing using a q-value adjustment, with the R program V.2.15.2, package 'qvalue'[97] (qvalue: Q-value estimation for false discovery rate control (program), R package version 1.32.0, 2014) which has been shown to be less stringent than the Bonferroni adjustment. All significance findings from LR and χ^2 (or Fisher's Exact test) reported herein refer to these adjusted values.

Inclusion and Logical Bounding

Only those factors that were identified by at least three of the four analyses employed and increased or decreased odds of MI by at least 40% were considered significantly associated with MI in this study and included herein. Furthermore, in order to address any bias that may have been created due to missing data (non-response) in this study, we performed a 'logical bounding' procedure in which we logically filled in missing data points in our data set, first with all participants who were not included due to missing values coded as 'yes' for MI and then as 'no' for MI. We then reran our LR analyses in order to see if our 'overall' factors associated with MI remained statistically significant and thereby determine if our results were robust. All p values generated from this logical bounding were also adjusted for multiple testing using q-value adjustment.

RESULTS

To assess changes in MI-associated factors over a person's lifetime, separate analyses were performed on individuals who ever had a MI up to 72 years of age compared to those who had a MI between 65 and 72 years of age (see the 'Methods' section). Participants included in the 'MI by 72 years of age' dependent variable were 47.4% men, had an average IQ of 102.1 with an average 13.75 years of regular education. At the time of the 2004 interview, the average age of participants was 64.3 years, 78.6% were married, with an average total household income of US$30,619. 11.6% of participants were smokers, consumed alcohol on average 7.6 days/month, and 12.5% have ever reported a MI to the WLS (see table 1). Of these participants, 85.9% were also included in the 'MI between 65 and 72 years of age' dependent variable. Men in the WLS were significantly more likely to experience MI than were women, to have more education, to be married, to have a higher household income and to drink alcohol more days per month than women in the WLS (table 1; based on t-test or equal proportions test). All analyses identified sex as the factor most associated with MI (see online supplementary

information 2), therefore men and women were analysed separately throughout this study. Note to readers: we reported results in terms of MI 'by 72' years and MI 'between 65 and 72' years because the majority of participants were 65 or younger during the 2004 survey and 72 or younger during the 2011 survey.

Men
MI up to age 72
Interactive effects
RP analysis indicated that 18.1% of men in this study reported a MI by age 72. High cholesterol by 65 years old was the most significant factor associated with MI among men according to RP (figure 1), with a prevalence of 23.1% versus 8.4% (OR 3.29, 95% CI 2.59 to 4.18). For men with normal cholesterol at 65, the interactions among factors associated with the largest increase in MI prevalence were being diabetic by 65, summary score for openness at 65 and genotype for the CYP11B2 gene (rs1799998 SNP), increasing MI prevalence to 30.6% versus 0.0% (20.22, 1.15 to 355.10). For men with normal cholesterol who were non-diabetic at 65, important interactions included their summary score for (psychological) distress/depression at 65 and having high blood pressure by 65, with MI prevalence at 27.5% versus 7.5% (4.66, 1.90 to 11.38). Among those men with a lower summary score for depression, important interactions included having high cholesterol by 72 and lower alcohol consumption at 72, with MI prevalence at 26.9% versus 4.4% (6.89, 2.12 to 22.44).

For men who did have high cholesterol by 65, important interactions among factors associated with MI include the number of years the participant had smoked by 54, alcohol consumption at 65, exposure to dangerous work conditions at 65 and genotype for the FADS2 gene (rs174575 SNP), with MI prevalence at 46.7% versus 7.1% (11.38, 1.96 to 66.12). For men who had high cholesterol by 65, but had smoked fewer years by 54, important interactions included being diabetic by 65, the extent to which one agreed that family worries or problems distracted from work at 65 and total years of college completed, with MI prevalence increased to 53.3% versus 0.0% (19.34, 1.02–365.26). For the men who did have high cholesterol by 65, but smoked fewer years by 54 and were non-diabetic at 65, important interactions among factors included having a biological parent or sibling who had a MI before age 55, the most he ever weighed in pounds by 72, total household income at 65 and genotype for the IL6 gene (rs1800795 SNP), with MI prevalence at 32.6% versus 5.3% (8.69, 1.83 to 41.36) (figure 1).

Single factor effects
For men up to 72 years old, the 10 most 'important' factors associated with MI determined using RF were as follows: (1) days/month drinking alcohol, (2) total household income, (3) dissatisfaction with financial situation, (4) alcoholic drinks/month, (5) high blood

pressure, (6) number of children, (7) high cholesterol, (8) the frequency that work required physical effort, (9) pack-years smoked and (10) worrying a lot, each at 72 years old (see online supplementary figure 1 for additional 'important' factors associated with MI by RF).

Of the factors that were associated with MI by RP or RF, LR identified having high cholesterol by 65 (3.29, 2.59 to 4.18) and 72 (3.32, 2.50 to 4.42), diabetes by 65 (3.24, 2.53 to 4.15) and 72 (2.26, 1.78 to 2.88), stroke by 65 (5.01, 3.36 to 7.48), high blood pressure by 65 (2.39, 1.92 to 2.96) and 72 (2.16, 1.67 to 2.79), exposure to dangerous conditions at work at 65 (1.41, 1.11 to 1.79) and having a parent or sibling who had a MI before age 55 (1.89, 1.43 to 2.49) as significantly associated with MI for men in this study (table 2A). χ^2 also identified these factors as significantly associated with MI.

Overall associations with MI by 72 years of age
Factors identified by at least three of the analyses employed by this study as associated with MI were compiled in order to determine which factors were most associated with MI in the WLS cohort. For men who had a MI any time up to 72 years of age, the factors associated with MI by all four analyses were having high cholesterol by 65, having high cholesterol by 72 and being diabetic by 65, which were all highly significant by LR and χ^2 (table 2A). These results are supported by the male RP tree, as having high cholesterol by 65 and being diabetic by 65 were the first and second nodes in that tree (figure 1). The factors that were associated with MI by three of the analyses in this study including RF were being diabetic by 72, having had a stroke by 65 and having high blood pressure by 72, which were all highly significant by LR and χ^2. The factors that were associated with MI by three of the analyses including RP were having high blood pressure by 65, exposure to dangerous conditions at work at 65 and having a parent or sibling who had a MI before age 55, which were all significant by LR and χ^2 (table 2A).

MI between 65 and 72 years of age
Interactive effects
In the second set of analyses, 5.9% of men reported a MI between 65 and 72 years of age. Days/month drinking alcoholic beverages at 65 years old was the only significant factor identified as associated with MI among men 65–72 according to RP (figure 2), with incidence at 7.7% among those who drank<8.5 days/month versus 2.9% among those who drank ≥8.5 days/month (2.77, 1.80 to 4.25).

Single factor effects
For men between 65 and 72 years of age, the 10 most 'important' factors associated with MI determined using RF were: (1) alcoholic drinks/month at 65 years old, (2) summary score for distress/depression at 54, (3) body mass index at 54, (4) alcoholic drinks/month at 54, (5) summary score for neuroticism at 54, (6) the most ever weighed (by 65), (7) days/month drinking alcohol at
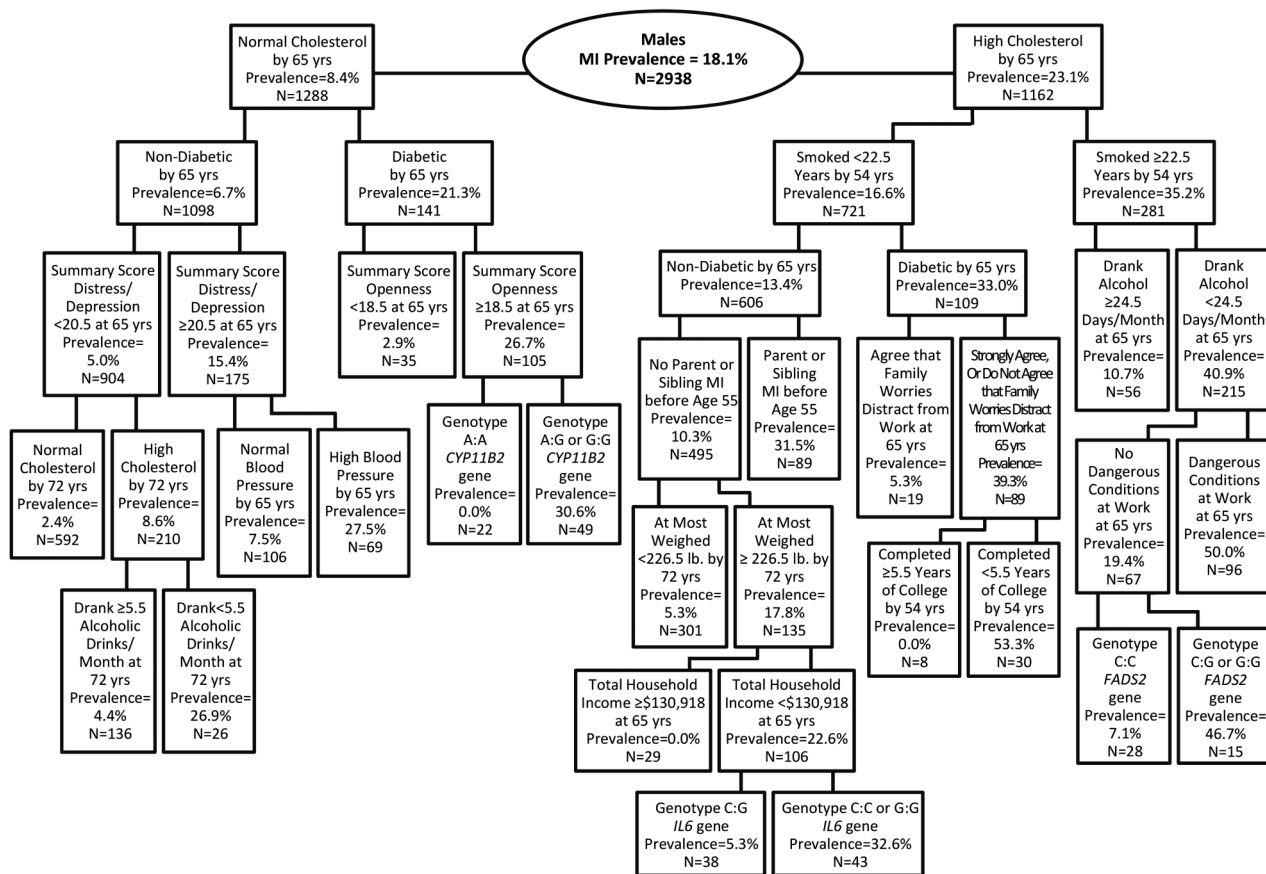
Figure 1 RP tree showing interactions among MI-associated factors for men who ever had a MI by 72 years of age in the WLS cohort, with MI prevalence listed at each node in the tree. MI, myocardial infarction; RP, recursive partitioning; WLS, Wisconsin Longitudinal Study.

65, (8) body mass index at 65, (9) pack-years smoked at 54 and (10) years smoked at 54 (see online supplementary figure 2 for additional 'important' factors associated with MI by RF).

Of the factors that were associated with MI by RP or RF, LR identified having had a stroke by 65 (4.08, 2.17 to 7.65) and being diabetic by 65 (2.71, 1.81 to 4.04) as significantly associated with MI for men 65–72 years old (table 2B). χ^2 also identified these two factors as significantly associated with MI for men in this age group (table 2B).

Overall associations with MI between 65 and 72 years of age
For men between 65 and 72 years old, the factors associated with MI by at least three of the four analyses employed by this study were having had a stroke by 65 and being diabetic by 65, which were highly significant by LR and χ^2 and 'important' factors by RF (table 2B).

Women
MI up to age 72
Interactive effects
RP analysis indicated that 7.5% of women in this study reported a MI by age 72. For women, being diabetic by 65 was the most significant factor associated with MI

according to RP, with a prevalence of 22.4% versus 4.9% (5.62, 4.08 to 7.75; figure 3). For the latter group, important interactions among factors associated with MI included high blood pressure by 65 and how often they engaged in light physical activities with others at 67, with MI prevalence at 3.7% versus 0.2% (18.39, 2.49 to 135.77). And among the women who were non-diabetic, but did have high blood pressure by 65, important interactions included how many years they had smoked by age 54, with MI prevalence at 16.6% versus 5.1% (3.70, 2.30 to 5.94), and how often the participant blamed themselves when they experienced a difficult or stressful event at 72 years old, with MI prevalence at 11.8% versus 2.7% (4.87, 2.25 to 10.55; figure 3).

Single-factor effects
For women up to 72 years old, the 10 most 'important' factors associated with MI determined using RF were as follows: (1) days/month drinking alcohol at 72, (2) dissatisfaction with financial situation at 72, (3) total household income at 72, (4) high blood pressure by 72, (5) worrying a lot at 72, (6) alcoholic drinks/month at 72, (7) being diabetic by 65, (8) number of children, (9)

Table 2 MI-associated factors for men found significant by at least three of the four statistical analyses employed by this study, (A) who ever had an MI by 72 years of age and (B) who had a MI between 65 and 72 years of age.

Factor description (age at survey year)	MI case/ non-case (n)	Random forest 'important' variables	Logistic regression OR (95% CI)	χ^2 (adjusted p value)	Recursive partitioning (tree nodes)
(A) Males, 'MI by 72 years of age'					
High cholesterol (by 65 years)	269/893	Yes	3.29 (2.59 to 4.18)***	<0.0001[C]	Present
High cholesterol (by 72 years)	221/987	Yes	3.32 (2.50 to 4.42)***	<0.0001[C]	Present
Diabetes (by 65 years)	124/254	Yes	3.24 (2.53 to 4.15)***	<0.0001[C]	Present
Diabetes (by 72 years)	122/458	Yes	2.26 (1.78 to 2.88)***	<0.0001[C]	
Stroke (by 65 years)	48/56	Yes	5.01 (3.36 to 7.48)***	<0.0001[C]	
High blood pressure (by 72 years)	269/1428	Yes	2.16 (1.67 to 2.79)***	<0.0001[C]	
High blood pressure (by 65 years)	283/1023		2.39 (1.92 to 2.96)***	<0.0001[C]	Present
Exposed to dangerous conditions at work (by 65 years)	174/784		1.41 (1.11 to 1.79)**	0.0080[C]	Present
Parent or sibling had a MI before age 55 (by 65 years)	82/267		1.89 (1.43 to 2.49)***	<0.0001[C]	Present
(B) Males, 'MI between 65 and 72 years of age'					
Stroke (by 65 years)	13/55	Yes	4.08 (2.17 to 7.65)***	0.0002[F]	
Diabetes (by 65 years)	36/254	Yes	2.71 (1.81 to 4.04)***	<0.0001[C]	

The 'age at survey year' of 65 and 72 represent survey years 2004 and 2011, respectively. Analyses associated with the 'MI by 72 years of age' data set included independent variables from all WLS survey years, 1957–2011, while analyses associated with the 'MI between 65 and 72 years of age' data set included only independent variables from WLS survey year 2004 or earlier.
'***'=p<0.001, '**'=p<0.01.
C, χ^2 test; F, Fisher's Exact test.

'MI Between 65-72 Years of Age' MI Associated Factors for Males
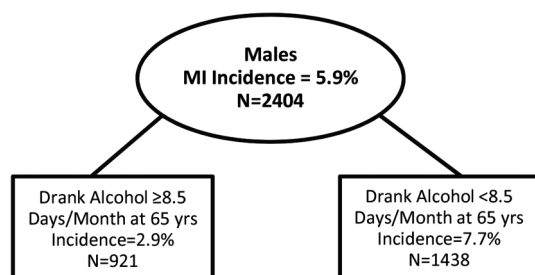
Figure 2 RP tree showing the only factor associated with MI by RP for men between 65 and 72 years of age in the WLS cohort, with MI incidence listed at the terminal nodes of the tree. MI, myocardial infarction; RP, recursive partitioning; WLS, Wisconsin Longitudinal Study.

body mass index at 72 and (10) the most ever weighed (by 72) (see online supplementary figure 3 for additional 'important' factors associated with MI by RF).

Of the factors that were associated with MI by RP or RF, LR identified being diabetic by 54 (6.93, 4.18 to 11.49), 65 (5.62, 4.08 to 7.75) and 72 (4.24, 3.04 to 5.91), high cholesterol by 72 (2.03, 1.38 to 3.00) being unmarried at 72 (1.59, 1.16 to 2.18), dissatisfaction with financial situation at 72 ((not at all) 4.00, 1.94 to 8.27; (somewhat) 2.02, 1.31 to 3.12; multiple coefficients significant by LR), not often engaging in vigorous physical activity alone at 67 (0.53, 0.32 to 0.89), high blood pressure at 65 (3.21, 2.34 to 4.39) and 72 (3.37, 2.23 to 5.09) and not often engaging in light physical activity with others at 67 (0.34, 0.21 to 0.57) as significantly associated with MI for women in this study (table 3A). χ^2 also identified these factors as significantly associated with MI (table 3A).

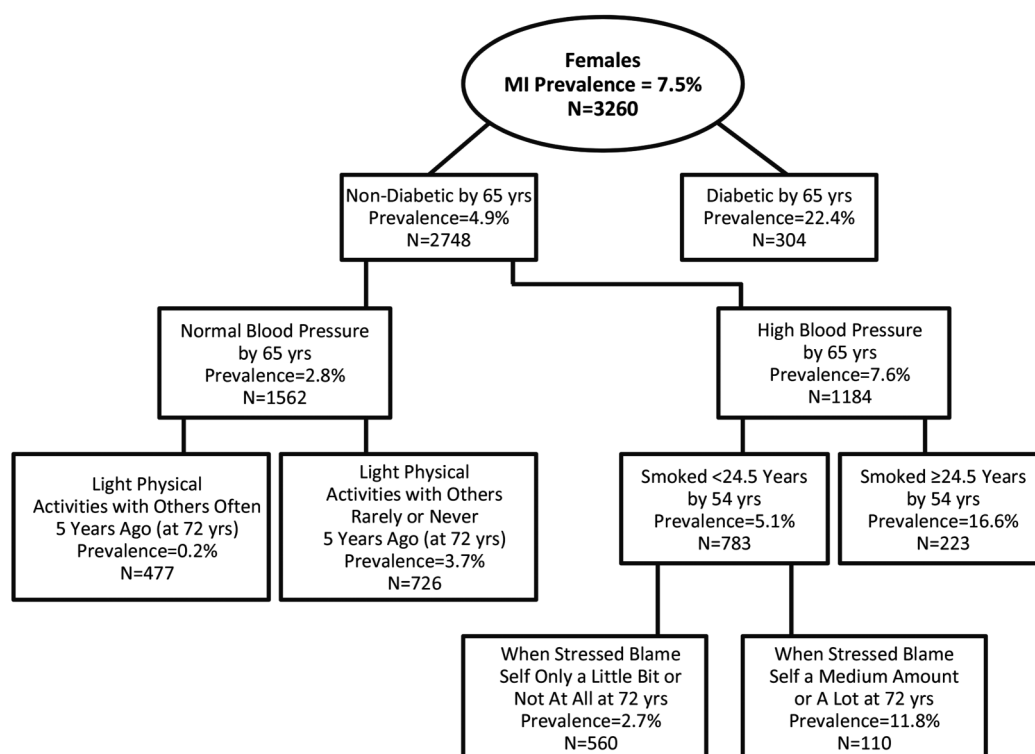### Overall associations with MI by 72 years of age

For women who reported a MI any time up to 72 years of age, the factor associated with MI by all four analyses was being diabetic by 65 years old, which was highly significant by LR and χ^2 (table 3A), and was the most associated factor according to the female RP tree (figure 3). The factors associated with MI by three of the analyses in this study including RF were being diabetic by 54 and 72, having high cholesterol by 72, being unmarried at 72, dissatisfaction with financial situation at 72, not often engaging in vigorous physical activity alone at 67 and having high blood pressure at 72, which were all significant by LR and χ^2. The factors associated with MI in women by three of the analyses in this study including RP were having high blood pressure by 65 and not often engaging in light physical activity with others at 67, which were both highly significant by LR and χ^2 (table 3A).

MI between 65 and 72 years of age
Interactive effects

In the second set of analyses, 2.5% of women reported a MI between 65 and 72 years of age. Being diabetic by 65 years old was again the most significant factor associated with MI among women in this age bracket according to RP (figure 4), with a MI incidence of 7.8% versus 2.0% (4.25, 2.50 to 7.24). For women who were diabetic

'MI by 72 Years of Age'
MI Associated Factors for Females

Figure 3 RP tree showing interactions among MI-associated factors for women who ever had a MI by 72 years of age in the WLS cohort, with MI prevalence listed at each node in the tree. MI, myocardial infarction; RP, recursive partitioning; WLS, Wisconsin Longitudinal Study.

by 65 years old, important interactions among factors associated with MI included their summary score for agreeableness at 65 and not having had a menstrual period in the last 12 months by 54 years of age, increasing MI incidence to 14.0% versus 0.0% (13.58, 0.79 to 233.29). For those women who were non-diabetic at 65, important interactions included IQ, genotype for the *INHBB* gene SNP (rs11902591) and how often their work required physical effort at 54, with MI incidence at 25.0% versus 0.0% (37.95, 1.81 to 795.67). And among those women with a lower IQ score, important interactions included their summary score for extraversion at 54, how often they engaged in light physical activities alone at 65, the number of alcoholic drinks consumed per month at 65, body mass index at 65, genotype for the A2M gene (rs669 SNP), how often they worked under the pressure of time at 54 and the age at which they had last menstruated, with MI incidence increasing to 13.8% versus 0.0% (12.42, 0.72 to 215.47) (figure 4).

Single factor effects

For women between 65 and 72 years of age, the 10 most 'important' factors associated with MI determined by RF were as follows: (1) alcoholic drinks/month at 65 years old, (2) summary score for distress/depression at 65, (3)

being diabetic by 65, (4) body mass index at 65, (5) the most ever weighed (by 65), (6) days/month drinking alcohol at 54, (7) days/month drinking alcohol at 65, (8) drinks/day on days when drank alcohol at 65, (9) age when had surgery to remove uterus and/or ovaries and (10) summary score for distress/depression at 54 (see online supplementary figure 4 for additional 'important' factors associated with MI by RF).

Of the factors associated with MI by RP or RF, LR identified being diabetic by 65 (4.25, 2.50 to 7.24), exposure to dangerous work conditions at 54 (2.24, 1.36 to 3.69) and having had a menstrual period in the last 12 months at 54 (0.46, 0.23–0.91) as significantly associated with MI for women between 65 and 72 years of age (table 3B). χ^2 also identified these factors as significantly associated with MI for women in this age group (table 3B).

Overall associations with MI between 65 and 72 years of age

For women between 65 and 72 years old, the factor associated with MI by all four analyses was being diabetic by 65, which was highly significant by LR and χ^2 (table 3B), and was the factor most associated with MI according to the female RP tree for this age group (figure 4). The factors associated with MI by at least three of the analyses employed in this study were exposure to dangerous

Table 3 MI-associated factors for woman found significant by at least three of the four statistical analyses employed by this study, (A) who ever had an MI by 72 years of age and (B) who had a MI between 65 and 72 years of age.

| Factor description (age at survey year)	MI case/ non-case (n)	Random forest 'important' variables	Logistic regression OR (95% CI)	χ^2 (adjusted p value)	Recursive partitioning (tree nodes)
(A) Females, 'MI by 72 years of age'					
Diabetes (by 65 years)	68/236	Yes	5.62 (4.08 to 7.75)***	<0.0001^C	Present
Diabetes (by 54 years)	24/55	Yes	6.93 (4.18 to 11.49)***	<0.0001^C	
Diabetes (by 72 years)	64/406	Yes	4.24 (3.04 to 5.91)***	<0.0001^C	
High cholesterol (by 72 years)	89/1354	Yes	2.03 (1.38 to 3.00)***	0.0007^C	
Unmarried (by 72 years)	77/1079	Yes	1.59 (1.16 to 2.18)**	0.0070^C	
Financial situation – 'not at all' satisfied (by 72 years)†	11/73	Yes	4.00 (1.94 to 8.27)***	0.0002^F	
Financial situation – 'somewhat' satisfied (by 72 years)†	67/879		2.02 (1.31 to 3.12)**	0.0002^F	
Vigorous physical activity alone 5 years ago - often (by 72 years)	21/639	Yes	0.53 (0.32 to 0.89)*	0.0330^C	
High blood pressure (by 72 years)	134/1769	Yes	3.37 (2.23 to 5.09)***	<0.0001^C	
High blood pressure (by 65 years)	145/1260		3.21 (2.34 to 4.39)***	<0.0001^C	Present
Light physical activity with others 5 years ago - often (by 72 years)	23/876		0.34 (0.21 to 0.57)***	0.0002^C	Present
(B) Females, 'MI between 65 and 72 years of age'					
Diabetes (by 65 years)	20/236	Yes	4.25 (2.50 to 7.24)***	<0.0001^C	Present
Exposed to dangerous conditions at work (by 54 years)	28/658	Yes	2.24 (1.36 to 3.69)**	0.0030^C	
Menstruated in last 12 months (by 54 years)	10/740		0.46 (0.23 to 0.91)*	0.0324^C	Present

The 'age at survey year' of 54, 65 and 72 represent survey years 1993, 2004 and 2011, respectively. Analyses associated with the 'MI by 72 years of age' data set included independent variables from all WLS survey years, 1957–2011, while analyses associated with the 'MI between 65 and 72 years of age' data set included only independent variables from WLS survey year 2004 or earlier.

'***'=p<0.001, '**'=p<0.01, '*'=p<0.05.

†Multiple coefficients found significant for this variable using logistic regression.

C, χ^2 test; F, Fisher's Exact test.
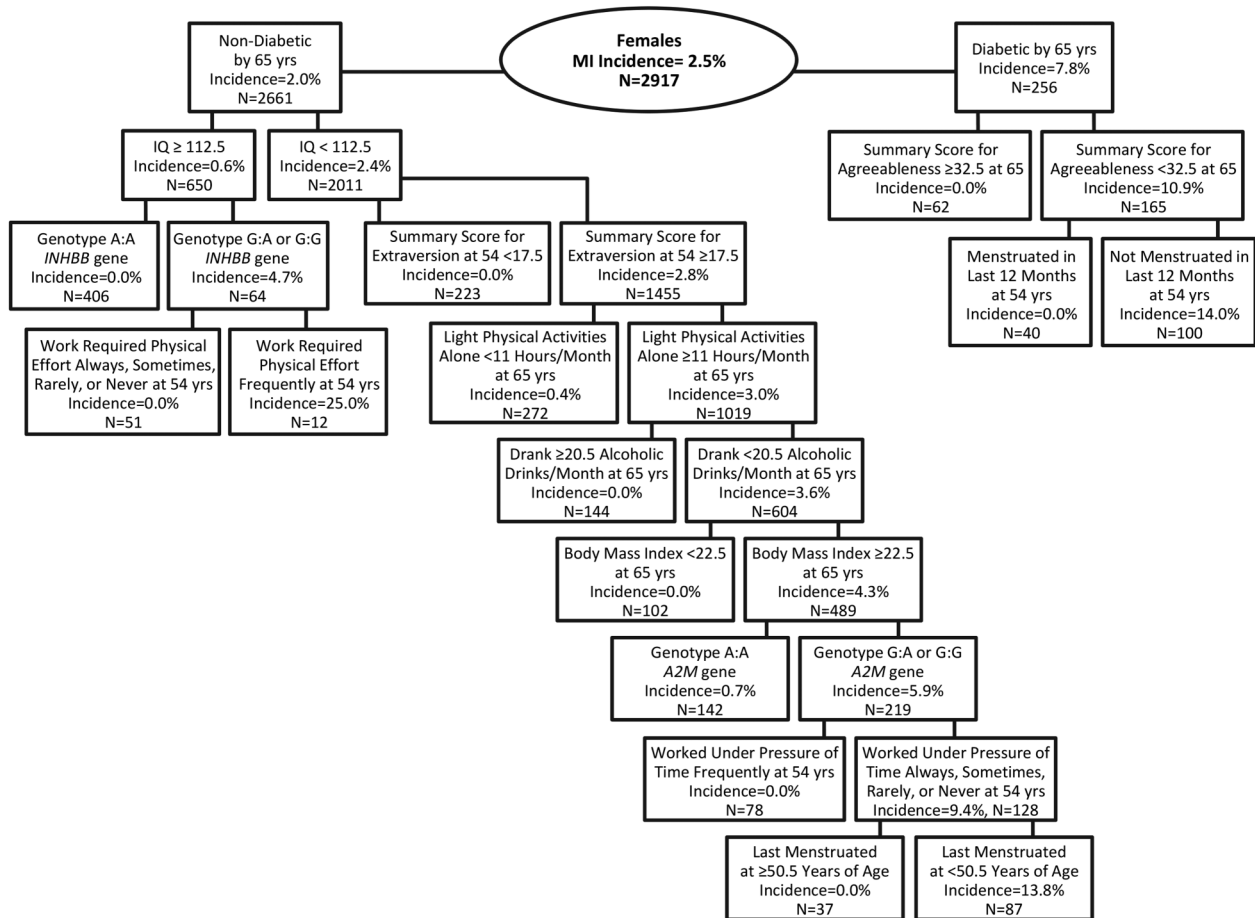
Figure 4 RP tree showing interactions among MI-associated factors for women who had a MI between 65 and 72 years of age in the WLS cohort, with MI incidence listed at each node in the tree. MI, myocardial infarction; RP, recursive partitioning; WLS, Wisconsin Longitudinal Study.

work conditions at 54, which was significantly associated with MI by LR and χ^2 and deemed an 'important' factor by RF, and having menstruated in the last 12 months at 54, which was significantly associated by LR and χ^2 and present in the RP tree (table 3B).

SNP associations with MI
None of the genetic variables tested appeared among the RF 'important' factors in any of the groups analysed. Although this study found several SNPs that were associated with MI by RP, specifically the *CYP11B2* (rs1799998), the *FADS2* (rs174575) and the *IL6* (rs1800795) gene SNPs in men up to 72, and the *INHBB* (rs11902591) and *A2M* (rs669) gene SNPs in women between 65 and 72 years, none of these were significantly associated with MI according to LR or χ^2 after adjustment for multiple testing.

Logical bounding
Logical bounding of missing data and subsequent LR analysis (see the 'Methods' section) showed that all but one of the factors associated with MI identified by

this study were robust to missing data, as they all remained statistically significant on both sides of the logical bounding procedure (results not shown). The only factor that did not remain significant was exposure to dangerous work conditions for women who had a MI between 65 and 72 years of age, when all missing data points were coded as 'yes', suggesting that this result was less robust or more sensitive to missing data, which should be considered when evaluating the results.

DISCUSSION
This study identified factors associated with MI among participants in the WLS. For men, the factor most associated with reported MI by 72 years old was having had a stroke by 65. High cholesterol, diabetes, high blood pressure and family history were also identified as top factors for men up to 72 years, as well as exposure to dangerous working conditions, which has not previously been identified as associated with MI in men. Stroke and diabetes by 65 were most associated with MI in men over

65 years in the WLS cohort. We identified being diabetic by 65 as the factor most associated with reported MI in women up to 72 years old. High cholesterol, being unmarried, dissatisfaction with finances, not engaging in physical activity and high blood pressure were also identified as associated with MI in women up to 72 years. Among women who had their MI after age 65, being diabetic remained the most associated factor. However, exposure to dangerous working conditions, also newly associated with MI in women, and whether they were still menstruating at 54 were also determined to be associated with MI for women in this group. For most of the factors listed, exposure time had a large effect on MI occurrence, for men and women in the WLS cohort. Interactions among these and other factors greatly affected MI occurrence in men and women. Furthermore, results showed that for men and women, not only do the MI-associated factors become less associated as people age, but many of the factors change or are different between younger and older people.

Men
MI by 72 years of age

Results showed that 18.1% of men reported a MI to the WLS by age 72. Stroke by 65 was associated with the greatest increase in LR odds of MI among these men (table 2A). The other factors associated with MI in this group include having high cholesterol, diabetes, high blood pressure, exposure to dangerous working conditions and having a parent or sibling who had a MI before age 55. Stroke has been cited as a risk factor for MI,[98 99] and MI has been established as a risk factor for stroke in prior studies,[100–102] and according to the American Stroke Association[103] stroke risk is doubled among those who have experienced MI due to atherosclerosis. Furthermore, high cholesterol, diabetes and high blood pressure represent three of the four conventional 'key' risk factors for MI, and their association with heart disease and MI risk is well characterised in the literature.[4–6 9 10 104] A family history of heart disease has been shown to be a significant contributor to MI risk in previous studies.[61 62 105 106] However, our study is the first to identify a link between exposure to dangerous working conditions and MI. Consistent with this, a number of studies show that stress in the workplace is associated with an increased risk of MI.[49 107–109] The increased odds of MI noted with a diagnosis by 65 years old rather than 72 (among above factors) suggest that exposure time is an important determinant in whether one experiences a MI or not. Although in this particular cohort having high cholesterol increased one's odds of MI by 3.3-fold, regardless of whether it was diagnosed by 65 or 72, prior studies have shown that those who are diagnosed with high cholesterol at a younger age (<50 years) are more likely to experience heart disease in their lifetime.[110–112]

This study demonstrates that interactions among factors associated with MI lead to large changes in MI prevalence (figure 1). While combinations of high cholesterol, diabetes, smoking and lower alcohol consumption were associated with increased prevalence and interacted with lesser-known factors such as depression, genetic factors, and dangerous working conditions to increase prevalence up to 50%, other factors including increased alcohol consumption, higher household income and higher education tended to lower prevalence, in some cases down to 0.0% even when other top MI risk factors were present. For example, high cholesterol, smoking and being diabetic are associated with higher MI prevalence, but for the subset of men who completed more than 5.5 years of college, prevalence in the WLS dropped to 0.0% compared to those completing <5.5 years of college, whose MI prevalence was a whopping 53.3%. This suggests that factors should not be evaluated individually, but rather the interaction among factors has to be considered when determining associations with MI (additional discussion of RP results can be found in online supplementary information 3).

MI between 65 and 72 years of age

Only 5.9% of men reported a MI between 65 and 72 years to the WLS, versus 18.1% who ever reported MI by 72 years, therefore the majority of MIs reported by men to the WLS and included in this study occurred before age 65. The factors most associated with MI for men between the ages of 65 and 72 years were having had a stroke and being diabetic, both by 65 years old (table 2B). These two factors were identified by both analyses of MI in men, suggesting that these factors are strongly associated with MI in men at any age. Interestingly, the odds of MI in the first analysis for men who ever had a MI by 72 were increased compared to the odds of MI between 65 and 72 years old, both for having had a stroke by 65 (5.0-fold vs 4.1-fold increase, respectively) and for being diabetic by 65 (3.2-fold vs 2.7-fold increase, respectively), suggesting that the key risk factors for MI become less predictive as men age, as supported by previous studies.[5 55] Additionally, the loss of two factors associated with MI in men from the first analysis, having high cholesterol or having high blood pressure (table 2B), suggests that factors associated with MI are different in younger versus older men. This result is supported by the fact that RP analysis identified fewer days/month drinking alcoholic beverages at 65 as the only factor affecting MI among men 65–72 years old, with a 2.7-fold increase in odds of MI among those who drank alcohol <8.5 days/month (7.7% vs 2.9%; figure 2). This supports prior studies proposing an insulating effect of regular moderate alcohol consumption, specifically in older adults (≥65 years),[113–115] but still suggests that the 'known' risk factors for MI change with age, at least for men in the WLS cohort.

Women

MI by 72 years of age

This study found that 7.5% of women reported MI to the WLS by age 72, which was 10.6% less than that reported in men for this age group. LR ORs indicated that being diabetic by 54 was associated with the greatest increase in odds of MI (table 3A). The other factors associated with MI for women in this group include being diabetic (any age), having high cholesterol, being unmarried, dissatisfaction with financial situation, not engaging in physical activity and having high blood pressure. Being diabetic (by 65) was also the single most important factor for MI among women up to 72 according to RP results (figure 3), with a 4.6-fold increase in MI prevalence among diabetic women (22.4% vs 4.9%). Diabetes has been shown in prior studies to be a strong predictor of MI risk in women.[116] As seen in men in this study, high cholesterol and high blood pressure are strongly associated with MI risk in women, as supported by previous studies. Marriage is a well-accepted indicator of MI risk and an even better indicator of one's recovery and health after experiencing an MI.[117–122] Dissatisfaction with one's financial situation was linked with MI risk in women in one prior study,[123] and another study showed an association between 'perceived financial status' and MI risk among employed women.[124] Dissatisfaction with one's financial situation could also be associated with financial stress, which has been linked to increased MI risk in multiple studies.[49 55 125] Reduced prevalence of MI in women in the WLS cohort who engaged in physical activity when they were about 67 years old is supported by numerous studies on the effects of physical inactivity and MI risk.[3 5 40 55] An even larger reduction in MI prevalence was noted among those who often engaged in light physical activity with others when 67 (0.34) versus those who often engaged in vigorous physical activity alone when 67 (0.53), suggesting that type of physical activity is less important and spending time with others may play a larger role for women when it comes to reducing MI risk. This is supported by previous studies showing that for women having 'social support' decreases risk of MI.[126 127] Furthermore, our study suggests that physical inactivity may play a more important role for women than for men when it comes to MI (table 3A), specifically concerning MI in those <65 years old, as supported by previous studies.[55]

In addition to identifying being diabetic by 65 as the most associated factor for women up to 72 years in the WLS cohort (figure 3), RP analysis showed that among those women who were non-diabetic at 65, the interaction of having high blood pressure by 65 and smoking $\geq$24.5 years by 54 more than tripled MI prevalence, again demonstrating the importance of considering interactions among factors when predicting MI risk (additional discussion of RP results can be found in online supplementary information 4). As in men, our study suggests that exposure time to certain factors is an important determinant in whether a woman has a MI or not. For example, odds of MI increase for diabetic women, but the younger a woman is when she is diagnosed, the higher her odds for eventually experiencing a MI, with a 6.9-fold, 5.6-fold and 4.2-fold increase in odds among those diagnosed by 54, 65 and 72 years old, respectively (R^2=0.98). However, this association does not hold for all medical health conditions in women in the WLS. For example, high blood pressure by 54 was not associated with MI, but was associated with increased odds of MI at 65 years (3.2-fold), and this increase in odds remained stable at 72 years (3.4-fold). Further study will need to be conducted in order to determine the exact mechanisms by which exposure time affects one's odds of having a MI and which MI-associated factors are more susceptible to this effect.

MI between 65 and 72 years of age

Only 2.5% of women reported a MI between 65 and 72 years to the WLS—much lower than that noted among women who ever reported a MI by 72 years old (7.5%). The factor associated with the highest odds of MI for women in this age group was being diabetic by 65 years old (table 3B), similar to women who ever had a MI by 72 years. RP analysis confirmed diabetes as the top factor associated with MI among women 65 to 72 years old (figure 4), again suggesting that this is potentially the most important factor associated with MI in women. However, just as in men, this factor is more associated with MI among younger women, or including those <65 years old, with a 5.62-fold increase as compared to the 4.25-fold increase in odds among those who experienced a MI after 65 years old (table 3B). Even so, this remained the most important factor associated with MI among women in the WLS at any age. This result is in agreement with what is known about diabetes and MI risk for women, as it has been shown that being diabetic increases not only a woman's MI risk, but also her risk for fatal coronary heart disease, ischaemic stroke, cardiovascular mortality and all-cause mortality.[116 128–130]

Additionally and interestingly, exposure to dangerous conditions at work (at 54 years old) was determined to be associated with MI for women 65–72 years old (2.2-fold increase; table 3B), just as exposure to dangerous work conditions (at 65 years) was a top factor for men who ever had a MI by 72 years (1.4-fold increase; table 2A). This may represent a possible new risk factor for MI, although more research is needed to confirm this result. Still it suggests that not only do MI-associated factors become less associated as women age, but those factors may change between younger and older women. This is supported by the last MI-associated factor for women 65–72 years old, whether she still had her menstrual period at 54 (0.46-fold decrease in odds; table 3B). The age at which a woman experiences her last menstrual cycle affects the age at which large, lasting hormonal changes take place in her body and has a very large

impact on her ageing and overall health. Supporting the results of this study, it has been shown that the earlier a woman stops menstruating, the shorter her lifespan and the more health problems she will encounter in later years, including an increased risk of MI.[131–141] Indeed, we have previously demonstrated in the WLS that the earlier a woman stops menstruating, the shorter her lifespan will be (Yonker et al., 2013). Our results are further supported by studies showing that hormone replacement therapy can ameliorate the effects of natural or surgical menopause, specifically in younger women.[142 144] In other words, the longer a woman's hypothalamic-pituitary-gonadal axis remains in balance, the lower her odds of experiencing a MI later in life (between 65 and 72 years old). The 'exposure to dangerous conditions at work' factor was shown to be more sensitive to missing data points in our logical bounding procedure, therefore additional work is needed to follow-up on this finding. However, this same factor was identified in men and women in this study, lending support to our result.

Among those women 65–72 years old in the 'riskiest' group, those who were diabetic by 65, the interaction of being less agreeable and having stopped menstruating by 54 resulted in a doubling of MI incidence, while those who were more agreeable or who did still menstruate when they were 54 experienced no MI, despite having the top MI-associated factor for women (figure 4). Among women who were non-diabetic at 65, the interaction of three other identified factors was associated with an increased MI incidence to 25%—3.2 times higher incidence than that noted before the interaction (see the 'Results' section). These examples highlight the importance of interactions among factors when predicting one's MI risk (figure 4; additional discussion of RP results can be found in online supplementary information 5).

SNP associations with MI
Although this study found several SNPs that were associated with MI by RP, none of these were significantly associated with MI according to LR or χ^2 after adjustment for multiple testing. Interestingly, while some studies have found an association of CYP11B2 (rs1799998) and IL6 (rs1800795) with cardiovascular disease or MI,[145–152] other studies have not found an association.[153–156] Future genome-wide association studies will provide more definite data as to the role these SNPs play in the disease.

Limitations
Few studies have included the breadth of factors evaluated in the present study; however, despite high participant response rates to the WLS, our largest limitation was the loss of WLS participants due to the design of the two dependent variables, attrition from the WLS and missing data common to survey studies (see online supplementary table S1). If the population of participants excluded from the study was somehow different from the population included, it may have created a bias which could affect our results. However, as stated above,

missing data is a limitation in every observational study and is an unavoidable consequence of using longitudinal survey data. Furthermore, the logical bounding procedure we performed showed that all but one of the 'overall' MI-associated factors identified were robust to missing data, lending support to our results.

An additional limitation in this study is that it is likely that some reported MIs may have occurred before some of the independent variables were measured, specifically for the 'MI by 72 years of age' analyses. Our data set did not include the dates of occurrence of all independent variables, therefore it was impossible to run a 'time-to-event' or survival analysis on these data. However, we were interested in factors present in participants who ever experienced a MI in their lifetime (up to 72 years), regardless of when their MI occurred. Therefore, this part of our analysis is a case–control retrospective study. Owing to the mentioned complications with the first analysis, we completed a second analysis in which all of the independent variables occurred before the participant's reported MI. Although this design reduced the number of participants included in the second analysis, it allowed us to determine which factors are associated with MI before the MI occurs and therefore are potentially predictive of MI. This part of our analysis is a true cohort study.

Additional limitations of the current study include limitations associated with ICD codes in death records and limitations in death records recovered by the WLS. Furthermore, Rosamond et al[157] found that when MI are self-reported, the numbers are often an overestimation. Again, these limitations are an unavoidable consequence of using longitudinal survey data, but still must be considered when interpreting results. Additionally, the predictive value of our genetic data was limited because of user bias in selection of SNPs; other genetic variants that we did not examine in this study may have provided information about crucial interactions involved with MI. Furthermore, the WLS has social-factor homogeneities, such as participants being almost exclusively non-Hispanic white people with middle-class to upper-middle-class backgrounds. Future directions for research will involve using these same machine-learning methodologies on more complete genetic profiles, such as from genome-wide SNP or sequencing data, with which we will be able to explore all genetic interaction possibilities rather than a limited subset of variants.

CONCLUSIONS
It has previously been shown that at least one of four key risk factors—smoking, high blood pressure, high cholesterol or diabetes (mellitus)—was observed in more than 80–90% of patients experiencing MI, and all of these risks combined account for a population attributable risk >90% for all MI—for men and women, old and young, worldwide.[5 55] However, our study indicated that: (1) the main factors associated with MI are different between men (high cholesterol, diabetes, stroke, high

blood pressure and family history) and women (diabetes, high cholesterol, being unmarried, dissatisfaction with financial situation, physical inactivity, high blood pressure and loss of menstruation); (2) interactions among MI-associated factors have a large influence on MI occurrence; (3) factors associated with MI change and associations weaken after 65 years of age in both sexes and (4) the interaction of factors can be associated with large reductions in MI prevalence, to near zero, even in the presence of one or more of the 4 key risk factors for MI. In addition to identifying the above recognised factors associated with MI, we found one previously unidentified factor associated with MI (exposure to dangerous conditions at work) among WLS participants, which may represent a 'new' risk factor for MI. Larger genetic studies are required to elaborate on the modest genetic interactions identified in this study.

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Contributors CSA and TG conceptualised the study. CLR, PH and CSA collected saliva samples and performed genotyping analyses. TG, JAY, VC and CLR identified the variables and performed the statistical analyses on the Wisconsin Longitudinal Study data set. CSA, JAY and PH directed the statistical analyses. TG and CSA drafted the manuscript. All authors critically reviewed the manuscript and approved the final version.

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