

Midlife Cardiovascular Risk Factors and Late-Life Unrecognized and Recognized Myocardial Infarction Detect by Cardiac Magnetic Resonance: ICELAND-MI, the AGES-Reykjavik Study

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Background—Associations of atherosclerosis risk factors with unrecognized myocardial infarction (UMI) are unclear. We investigated associations of midlife risk factors with UMI and recognized MI (RMI) detected 31 years later by cardiac magnetic resonance.

Methods and Results—The Reykjavik Study (1967–1991) collected serial risk factors in subjects, mean (SD) age 48 (7) years. In ICELAND-MI (2004–2007), 936 survivors (76 (5) years) were evaluated by cardiac magnetic resonance. Analysis included logistic regression and random effects modeling. Comparisons are relative to subjects without MI. At baseline midlife evaluation, a modified Framingham risk score was significantly higher in RMI and in UMI versus no MI (7.4 (6.3%); 7.1 (6.2%) versus 5.4 (5.8%), $P<0.001$). RMI and UMI were more frequent in men (65%, 64% versus 43%; $P<0.0001$). Baseline systolic and diastolic blood pressure were significantly higher in UMI (138 (17) mm Hg versus 133 (17) mm Hg; $P<0.006$; 87 (10) mm Hg versus 84 (10) mm Hg; $P<0.02$). Diastolic BP was significantly higher in RMI (88 (10) mm Hg versus 84 (10) mm Hg; $P<0.02$). Cholesterol and triglycerides were significantly higher in RMI (6.7 (1.1) mmol/L versus 6.2 (1.1) mmol/L; $P=0.0005$; and 1.4 (0.7) mmol/L versus 1.1 (0.7) mmol/L; $P<0.003$). Cholesterol trended higher in UMI ($P=0.08$). Serial midlife systolic BP was significantly higher in UMI versus no MI (β [SE] = 2.69 [1.28] mm Hg, $P=0.04$). Serial systolic and diastolic BP were significantly higher in RMI versus no MI (4.12 [1.60] mm Hg, $P=0.01$ and 2.05 [0.91] mm Hg, $P=0.03$) as were cholesterol (0.43 [0.11] mmol/L, $P=0.0001$) and triglycerides (0.3 [0.06] mmol/L, $P<0.0001$).

Conclusions—Midlife vascular risk factors are associated with UMI and RMI detected by cardiac magnetic resonance 31 years later. Systolic blood pressure was the most significant modifiable risk factor associated with later UMI. (*J Am Heart Assoc.* 2016;5:e002420 doi: 10.1161/JAHA.115.002420)

Key Words: epidemiology • hypertension • magnetic resonance imaging • myocardial infarction • risk factors

Epidemiologic studies describe associations between baseline cardiovascular risk factors and subsequent clinically recognized myocardial infarction (RMI), typically reported as mortality from ischemic heart disease or composite cardiovascular end points that include MI.^{1–7} It is uncertain whether traditional risk factors for RMI also account fully for unrecognized MI (UMI) or whether UMI has additional

risk factors.^{8–11} By comparison with RMI, risk factors for development of UMI are less clearly defined because of inability to detect UMI accurately. Using usual diagnostic clinical criteria, there can be underreporting of UMI for several reasons including missed diagnosis, lack of symptoms, insensitivity of 12-lead ECG, or in some cases, regression of q waves with time.^{4,12–15} Therefore, UMI, which carries a

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significant risk of subsequent adverse cardiac events,^{16,17} may be underestimated for prospective modification of risk.^{11,17,18}

Advances in imaging by cardiac magnetic resonance (CMR) with late gadolinium enhancement allow more accurate detection of MI, including asymptomatic or unrecognized silent events.^{16,19,20} Indeed, CMR is the most accurate method available to detect myocardial scar and reports a higher prevalence of UMI^{16,17,21} than other technologies, making it more precise for population-based studies.²² The association of UMI detected by CMR with specific risk factors measured decades earlier has not been reported previously.

Between 1967–1991, the Icelandic Heart Association Reykjavik Study (Reykjavik) assessed vascular risk factors in a cohort of then middle-aged subjects born 1907–1935 and living in the Reykjavik region.²³ The study was extended in the Age Gene/Environment Susceptibility-Reykjavik Study (AGES 2002–2006) to evaluate phenotypes of aging in organ systems, including the cardiovascular system, in surviving cohorts of Reykjavik.²⁴ ICELAND-MI, a substudy of AGES, used CMR to detect MI scarring with a high degree of accuracy (2004–2007).¹⁶

The specific aim of this study was to investigate the association of cardiovascular risk factors measured at midlife with presence of UMI and RMI detected several decades later by CMR in ICELAND-MI. We hypothesized that (1) baseline midlife cardiovascular risk factors that are important for clinically RMI would also be associated with UMI detected at late life by accurate CMR methodology, and (2) serial midlife measures of cardiovascular risk factors would be associated with both UMI and RMI at late life.

Methods

The Icelandic Reykjavik Study was a cohort of 30 795 randomly selected subjects born between 1907 and 1935 living in the Reykjavik area in 1967. Serial cardiovascular measures and covariates were collected from the Reykjavik cohort between 1967 and 1996 to provide cross-sectional and longitudinal data. The AGES-Reykjavik Study (2002–2006) was designed to study 5764 subjects aged 66 to 98 years old randomly selected from the surviving Reykjavik cohort.²⁴ All participants signed a written informed consent and the study was approved by the National Bioethics Committee in Iceland and the Institutional Review Board of the Intramural Research Program of the National Institute on Aging.

In 2004, ICELAND-MI was initiated to investigate prevalence of vascular risk factors and the presence of RMI and UMI identified by late gadolinium enhancement CMR. The sample size for this cohort has been previously described (n=936).¹⁶ Recruitment occurred in 2 phases. Phase 1 was a

random sample of the AGES-Reykjavik cohort, which enrolled 702 subjects. Phase 2 enrollment specifically recruited subjects with diabetes and enrolled another 290 subjects. After exclusion of subjects who did not undergo the CMR and subjects with technical problems that prevented image analysis, the final sample size was 936 subjects for the current study.

Magnetic Resonance Imaging

All CMR studies were performed on a 1.5-T Signa Twinspeed scanner using a 4-element cardiac phased-array coil (General Electric Medical Systems, Waukesha, WI) as previously described.^{16,25} Images were acquired during breath-hold and triggered to the ECG or to pulse oximetry if ECG gating was suboptimal.

Late gadolinium enhancement imaging has been validated in both small and large animals, and in an international randomized controlled trial.^{26–29} Imaging was performed to evaluate MI scar, typically 6 to 15 minutes after injection of gadopentetate dimeglumine at low dose (0.1 mmol/kg; Magnevist, Schering AG, Berlin, Germany), using a phase-sensitive segmentation gradient echo inversion recovery sequence.²⁵ Calculated median glomerular filtration rate was 69 (interquartile range 59–82) mL/min per 1.73 m² and no subject had significant renal failure.^{16,30}

Using the 17-segment standardized model of the American Heart Association,³¹ the diagnosis of MI was based on consensus of 2 cardiologists experienced in CMR and blinded to subject clinical characteristics. For each segment, MI scar was considered present if the detected lesion had endocardial involvement and followed a coronary distribution. Scar patterns considered atypical for MI were not designated as MI. The size of left ventricular infarct was expressed as a percentage of total left ventricle.

Modifiable Risk Factors and Modified Framingham Score at Midlife

By design, a portion of the Reykjavik cohort were examined up to 5 times between 1967 and 1991²⁴ to document modifiable risk factors including lipid levels, blood pressure (BP), smoking, diabetes, obesity measured as body mass index, and physical activity. Other reported modifiable risk factors³² including psychosocial factors, nutrition, and alcohol use were not assessed in this study.

Serum cholesterol and triglycerides were measured after an overnight fast using a chemical colorimetric method.^{3,33,34}

Supine BP was measured twice in fasting subjects by a nurse after 5 minutes of rest between 8:30 AM and 10:30 AM. The mercury “Erkameter” wall-model sphygmomanometer (Erka, Germany) with cuff including a rubber bladder

15×32 cm, and total length 66 cm was used. BP was the average of the 2 measures.³⁵

Body mass index was calculated as weight (kilograms) divided by height² (meters). Physical activity was assessed using a questionnaire that asked about physical activity assessed as 1=never, 2=rarely, 3=occasionally, 4=moderate, 5=high.

A modified Framingham percentage risk was calculated using Framingham score variables that included age, gender, total cholesterol, smoking status, systolic BP, diabetes, and use of antihypertensive treatment, but excluded high-density lipoprotein cholesterol, which was not estimated in the Reykjavik Study.^{36,37}

Covariates

Covariates included demographic information (age, sex), and risk factors associated with cardiovascular events assessed at midlife included smoking history, glucose level, and use of antihypertensive drugs.

Statistical Analysis

An adjudication committee determined whether or not subjects had a clinically recognized MI (RMI) event based on subject history supported by hospital or surveillance records. Unrecognized MI (UMI) was defined as MI detected by CMR but without evidence of clinical RMI from hospital or surveillance records.¹⁶ The group without MI was the remainder of subjects who did not have a clinical event attributed to RMI by the adjudication committee or UMI detected by CMR.

Baseline characteristics at midlife were compared between groups first with and without MI, and then for RMI, UMI, or no MI using logistic regression adjusted for sex and midlife age, and then further adjusted for use of antihypertensive drugs, blood glucose, smoking, all at midlife, and age at late life. Multivariate analysis was performed by logistic regression to compare all MI versus no MI and by polynomial logistic regression to compare RMI and UMI with no MI.

Serial systolic and diastolic BP, serum cholesterol, and triglyceride courses were estimated visually by plotting mean values at each midlife measure, stratified by presence of RMI or UMI or no MI.

A random-effects model (with random intercept and slope function) was used to model the trends in midlife cardiovascular measures by presence of recognized, unrecognized, or no MI. This approach takes into account the correlation of within-individual measures, and the fact that there are unequal numbers of observations per individual. The random intercept and slope allow the estimates to vary on an individual level. Each model was tested for a significant interaction term between RMI or UMI and age to test whether

the slopes of the cardiovascular risk factors differ between the 3 groups.

The models were first adjusted for sex, and age at midlife and late life, and then further adjusted for midlife variables including smoking history (never versus ever), use of BP-lowering medication, and blood glucose.

Statistical analysis was performed using SAS 9.3 (SAS Institute Inc, Cary, NC). Data were expressed as mean (standard deviation) or percentage (number). In all analyses, the conventional α -level of 0.05 was used for significance testing. The mean per time point for each variable was plotted according to the presence or absence of MI using R software version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria).³⁸

The analytic sample consisted of 936 subjects described previously who completed the CMR examination on average 31 (3) years after the baseline Reykjavik visit.¹⁶ There were 1 or more assessments of risk factors in the subjects at midlife; 460 had 1 assessment, 185 had 2 assessments, 42 had 3 assessments, 93 had 4 assessments, and 156 had 5 assessments between 1967 and 1991. The subjects who came for 1 rather than for multiple visits were older (49.4 (6.4) versus 46.2 (7.9) years; $P<0.001$), and less likely to be men (43.1% versus 53.2%, $P=0.04$), but more likely to smoke (35.1% versus 8.8%, $P<0.001$), be diabetic (1.7% versus 0.2%, $P=0.05$), and to take antihypertensive agents (7.6% versus 1.0%, $P<0.001$; Table 1).

Results

Baseline Midlife Cardiovascular Risk Factors and Subsequent MI in Late Life

At late-life ICELAND-MI follow-up, the mean age of the group was 76.7 (5.3) years. Twenty-six percent (248/936) of subjects had MI when assessed by CMR in late life and of these, the majority were unrecognized (63%; 157/248), whereas 37% (91/248) of subjects had a clinically recognized event.¹⁶ Among clinically RMI, 22 subjects (24% RMI or 9% all MI) did not have evidence of myocardial scar by CMR, and 10/22 (45%) of these subjects had undergone a revascularization procedure.

At the baseline midlife assessment, the modified Framingham risk score was significantly higher in the entire MI group (7.2 [6.2]% versus 5.4 [5.8]%, $P<0.001$; Table 2). There were significantly more men in the MI group compared with the no MI group (64.1% versus 42.6%; $P<0.001$; Table 2). The MI group had a significantly higher systolic and diastolic BP (138 [16] versus 133 [17] mm Hg; $P=0.002$ and 87 [10] versus 84 [10] mm Hg; $P=0.002$), and serum cholesterol (6.52 [1.15] versus 6.24 [1.07] mmol/L; $P=0.001$). Serum triglycerides were significantly higher only after adjustment for sex and age at mid- and late life, and midlife covariates (1.31 [0.68] versus 1.12 [0.64] mmol/L, $P=0.03$).

Table 1. Characteristics of Subjects With One Versus Multiple Visits at Baseline Midlife Assessment in the Reykjavik Study

Characteristics at First BP Measurement, M (SD)	One Visit	Multiple Visits	P Value*
	n=459	n=477	
Age	49.4 (6.4)	46.2 (7.9)	<0.0001
Men, % (n)	43.1 (198)	53.2 (254)	0.04
Height, cm	170.4 (8.6)	171.9 (9.1)	0.26
Weight, kg	74.1 (12.6)	75.3 (13.1)	0.80
BMI, kg/m ²	25.4 (3.5)	25.4 (3.4)	0.41
Tobacco use, % (n)			
Ever smoker	58.8 (270)	14.3 (68)	<0.0001
Current smoker	35.1 (161)	8.8 (42)	<0.0001
Antihypertensive medication, % (n)	7.6 (35)	1.0 (5)	0.0003
Diabetes mellitus, % (n)	1.7 (8)	0.2 (1)	0.05
Blood pressure, mm Hg [†]			
Systolic	133.8 (17.2)	134.1 (16.8)	0.25
Diastolic	84.5 (10.2)	84.9 (10.1)	0.38
Blood sample			
Cholesterol, mmol/L	6.34 (1.14)	6.29 (1.06)	0.57
Triglycerides, mmol/L [‡]	1.18 (0.69)	1.16 (0.63)	0.84
Fasting glucose, mmol/L	80.3 (10.9)	80.5 (11.2)	0.54
Creatinine, μmol/L	85.4 (13.8)	85.5 (14.7)	0.08

BMI indicates body mass index; BP, blood pressure; M (SD), mean (standard deviation).

*Logistic regression to compare subjects with one or more than one visit, adjusted for age and sex.

[†]Adjusted for antihypertensive medications.

[‡]Adjusted for cholesterol.

The modified Framingham risk score was significantly higher in RMI and in UMI compared with no MI (7.4 [6.3]% and 7.1 [6.2]% versus 5.4 [5.8]%, $P=0.0003$; Table 3). The percentage of men was higher in RMI and in UMI than in no MI (Table 3). Baseline systolic BP was significantly higher in UMI, and trended higher in RMI ($P=0.06$). Baseline diastolic BP was elevated significantly in both RMI and UMI (Table 3). Serum cholesterol and triglycerides were significantly higher in RMI (Table 3). Serum cholesterol trended higher in UMI ($P=0.08$). When risk factors for RMI were compared with risk factors for UMI, there were not significant differences.

In a multivariate analysis of baseline midlife risk factors, gender, systolic BP, and serum cholesterol were all signifi-

Table 2. Baseline Characteristics of Population at Midlife by Presence of Late-Life Myocardial Infarction Detected by Cardiac MR at ICELAND_MI

General Characteristics, M (SD)	MI	No MI	P Value*
	N=248	N=688	
Age	48.1 (7.0)	47.7 (7.5)	<0.06
Men, % (n)	64.1 (159)	42.6 (293)	<0.001
Height, cm	172.7 (8.6)	170.6 (8.9)	0.08
Weight, kg	76.7 (12.8)	74.0 (12.8)	0.55
BMI, kg/m ²	25.6 (3.4)	25.4 (3.5)	0.84
Tobacco use, % (n)			
Ever smoker	35.5 (88)	36.3 (250)	0.38
Current smoker	23.8 (59)	20.9 (144)	0.44
Antihypertensive medication, % (n)	5.2 (13)	3.9 (27)	0.45
Diabetes mellitus, % (n)	0.4 (1)	1.2 (8)	0.37
Blood pressure, mm Hg [†]			
Systolic	138 (16)	133 (17)	0.002
Diastolic	87 (10)	84 (10)	0.002
Blood sample			
Cholesterol, mmol/L	6.52 (1.15)	6.24 (1.07)	0.001
Triglycerides, mmol/L [‡]	1.31 (0.68)	1.12 (0.64)	0.09
Fasting glucose, mmol/L	4.5 (0.5)	4.5 (0.6)	0.25
Creatinine, μmol/L	88.0 (17.6)	88.0 (17.6)	0.56
Midlife physical activity [§]	2.8 (1.3)	2.9 (1.3)	0.23
Modified Framingham % risk	7.2 (6.2)	5.4 (5.8)	<0.0001

BMI indicates body mass index; M (SD), mean (standard deviation); MI, myocardial infarction; MR, magnetic resonance imaging.

*Logistic models to compare the overall difference between the groups adjusted for age and sex.

[†]Adjusted for antihypertensive medications.

[‡]Adjusted for cholesterol.

[§]Exercise: 1=never, 2=rarely, 3=occasionally, 4=moderate, 5=high.

^{||}Model not corrected because age and sex are included in risk score.

cantly higher in all MI vs. no MI (Table 4). Similarly, sex, serum cholesterol, and triglycerides were significantly associated risk factors for RMI, whereas sex and systolic BP were the most significant factors for UMI (Table 4).

The percentage size of UMI was smaller than the percentage size of RMI (6 [7]% versus 14 [13]%, $P<0.0001$).

Serial Midlife Cardiovascular Risk Factors and Subsequent MI

Midlife BP and MI

Figure shows the trend in midlife systolic and diastolic BP and MI. In random effects models I and II, systolic BP was

Table 3. Baseline Characteristics of Population at Midlife by Presence of Late-Life Recognized or Unrecognized Myocardial Infarction Detected by Cardiac MR at ICELAND_MI

Baseline Midlife Risk Factors, M (SD)	Recognized MI	Unrecognized MI	No MI	P Value*
N	91	157	688	
Age	47.9 (6.6)	48.3 (7.2)	47.7 (7.48)	0.07
Men, % (n)	64.8 (59) [¶]	63.7 (100) [¶]	42.6 (293)	<0.0001
Height, cm	172.7 (8.9)	172.7 (8.5)	170.6 (8.9)	0.20
Weight, kg	75.9 (12.9)	77.1 (12.8)	74.0 (12.8)	0.49
BMI, kg/m ²	25.4 (3.5)	25.8 (3.4)	25.4 (3.5)	0.63
Tobacco use, % (n)				
Ever smoker	38.5 (35)	33.8 (53)	36.3 (250)	0.51
Current smoker	26.4 (24)	22.3 (35)	20.9 (144)	0.59
Antihypertensive medication, % (n)	3.3 (5)	5.1 (8)	3.9 (27)	0.68
Diabetes mellitus, % (n)	0	0.6 (1)	1.2 (8)	0.89
Blood pressure, mm Hg [†]				
Systolic	137.4 (15.1) [#]	138.3 (16.9) ^{**}	132.6 (17.0)	0.01
Diastolic	87.7 (9.8) ^{††}	87.2 (10.3) ^{††}	83.7 (10.0)	0.006
Blood sample				
Cholesterol, mmol/L	6.67 (1.14) ^{‡‡}	6.43 (1.15) ^{§§}	6.24 (1.07)	0.001
Triglycerides, mmol/L [‡]	1.40 (0.72)	1.25 (0.66)	1.12 (0.65)	0.009
Fasting glucose, mmol/L	80.2 (8.6)	80.6 (9.6)	80.3 (11.6)	0.48
Creatinine, μmol/L	89.2 (13.2)	88.4 (14.9)	84.3 (14.1)	0.77
Midlife physical activity [§]	2.6 (1.3)	2.9 (1.2)	2.88 (1.25)	0.18
Modified Framingham % risk	7.4 (6.3) ^{¶¶}	7.1 (6.2) ^{¶¶}	5.4 (5.8)	0.0003

BMI indicates body mass index; M (SD), mean (standard deviation); MI, myocardial infarction; MR, magnetic resonance imaging.

*ANOVA and logistic models to compare recognized MI and unrecognized MI with no MI adjusted for age and gender.

[†]Adjusted for antihypertensive medications.

[‡]Adjusted for serum cholesterol.

[§]Exercise: 1=never, 2=rarely, 3=occasionally, 4=moderate, 5=high.

^{||}Model not corrected for age and gender because these are included in the score.

[¶] $P \leq 0.0001$; [#] $P = 0.06$; ^{**} $P \leq 0.006$; ^{††} $P < 0.02$; ^{‡‡} $P = 0.0005$; ^{§§} $P = 0.08$; ^{|||} $P \leq 0.003$; ^{¶¶} $P < 0.05$.

consistently significantly higher by 3.2 mm Hg in the entire MI group ($P=0.003$; Table 5). Serial systolic BP was significantly higher for both RMI and UMI ($P=0.01$ and 0.04 , respectively; Figure, Table 5). Diastolic BP was consistently significantly higher by 1.5 mm Hg in the entire MI group ($P=0.02$; Figure, Table 5), but only RMI, not UMI, was the significant contributor to this finding.

Midlife serum cholesterol and triglycerides and MI

In random effects models I and II, serial cholesterol was significantly higher by 0.25 mmol/L in the entire MI group ($P=0.001$; Figure, Table 5). Similarly triglycerides were significantly higher by a mean of 0.15 mmol/L in the MI group ($P=0.02$; Figure, Table 5). For both cholesterol and triglycerides, only RMI was significantly related to blood levels in the models (Figure, Table 5).

Other modifiable risk factors and MI

There was no significant trend in midlife body mass index or blood glucose level and later MI (Table 5). Physical activity was marginally lower in RMI.

Discussion

In this cohort, midlife atherosclerotic risk determined using a modified Framingham risk score was associated significantly with all late-life MI. Importantly, the modified Framingham percentage risk score was significantly higher not only in RMI, but also in UMI. It is perhaps surprising that late-life RMI and UMI are associated strongly with a midlife summary risk score obtained 3 decades earlier and derived from single baseline measures of traditional risk factors, which could be prone to measurement errors and any interim personal changes.³⁹

Table 4. Multivariate Analysis of Baseline Midlife Risk Factors With Late-Life Myocardial Infarction Using Logistic Regression

Baseline Midlife Risk Factors	All MI*	Recognized MI*	Unrecognized MI*
	Odds Ratio (95% Confidence Interval)		
Age	1.02 (0.99, 1.04)	1.00 (0.96, 1.03)	1.03 (1.00, 1.05)
Sex	2.91 (1.88, 4.51)	2.69 (1.41, 5.12)	3.08 (1.83, 5.19)
Cholesterol	1.18 (1.01, 1.37)	1.39 (1.12, 1.72)	1.06 (0.89, 1.28)
Systolic BP	1.01 (1.00, 1.02)	1.01 (1.00, 1.03)	1.02 (1.00, 1.03)
BMI, kg/m ²	0.98 (0.94, 1.04)	0.95 (0.87, 1.02)	1.01 (0.95, 1.07)
Glucose	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
Serum creatinine	0.52 (0.14, 1.97)	0.89 (0.13, 6.04)	0.38 (0.08, 1.87)
Serum triglyceride	1.27 (0.99, 1.62)	1.40 (1.02, 1.93)	1.17 (0.87, 1.59)
Physical activity	1.09 (0.92, 1.29)	0.99 (0.77, 1.28)	1.15 (0.94, 1.41)
Hypertension medications	0.82 (0.38, 1.74)	0.76 (0.27, 2.26)	0.84 (0.34, 2.03)
Smoking	1.21 (0.87, 1.70)	1.08 (0.66, 1.76)	1.31 (0.87, 1.96)

BMI indicates body mass index; BP, blood pressure; MI, myocardial infarction.

*Compared with no MI group.

CMR is the most accurate technique available to detect myocardial scar whether recognized or unrecognized, and the presence of scar is associated with a worse prognosis.¹⁶ In earlier studies in which detection of MI was based on clinical and electrocardiographic findings, large numbers of subjects were needed to detect relationships.⁵ In this study, CMR detected recognized and unrecognized MI in 26% of subjects in this cohort of 936 subjects. A small percentage of clinically RMI subjects had normal CMR. Subjects with clinically RMI and yet no myocardial scar by CMR could be explained by revascularization, reversible pathology such as myocarditis, or a clinical misdiagnosis.

Midlife measures of systolic and diastolic BP and cholesterol were associated significantly with the presence of all late-life MI. Although many reports describe the association of hypertension with increased cardiovascular mortality,^{2,4,14,40–43} this unique data set links small increases in BP and cholesterol at midlife with UMI and RMI evaluated by CMR on average 31 years later.

In ICELAND-MI, serial midlife measures of both systolic and diastolic BP remained consistently higher in the MI group without a change in trend with time. Multiple factors may have contributed to persistent elevation of BP in the MI group including increasing age, changes in vascular compliance, and patient compliance with therapy.^{44–47} Although antihypertensive therapy reduces clinical MI in randomized controlled trials,⁴⁸ translation of trial results into effective control of BP during 25 years or more is challenging, despite increased drug therapy with time.¹⁶ Our results indicate that even minor elevations of BP in the prehypertension range may be a risk for later MI, and are consistent with recent data from the Chicago

Heart Association.⁴⁹ These data raise questions about target pressures recommended by recent European guidelines and US reports.^{50–52} The data may also be complementary to the SPRINT trial in which preliminary reports suggest that aggressive lowering of BP below current thresholds may be beneficial.⁵³

Both baseline and serial cholesterol levels were significantly associated with all later MI. There are no data on high-density lipoprotein cholesterol or on use of statins at midlife because these drugs were licensed in the late 1980s toward the end of the Reykjavik study. The association between serum triglycerides and all MI, independent of serum cholesterol, is consistent with prior combined mortality and morbidity data.^{54,55}

In this study, systolic BP was the most significant modifiable risk factor for UMI. There was also a trend for higher serum cholesterol in the UMI group. Equal prevalence of risk factors has been reported for both recognized and unrecognized MI detected by electrocardiographic criteria,¹¹ but our study differs from earlier reports because this is an older cohort of late-life survivors of the original Reykjavik study in whom MI was detected by CMR. Prevalence and risk factors of UMI demonstrate substantial variability, depending on the population under study.⁸

The size of unrecognized MI was smaller than RMI, a finding that has been reported in other studies.²¹ UMI shares some characteristics with silent cerebral infarctions, which are of smaller size in general, increase in prevalence with age, have few identified risk factors except age and hypertension, and portend later adverse cerebral events.^{56,57} Whether UMI differs from RMI by presence of small vessel disease or in

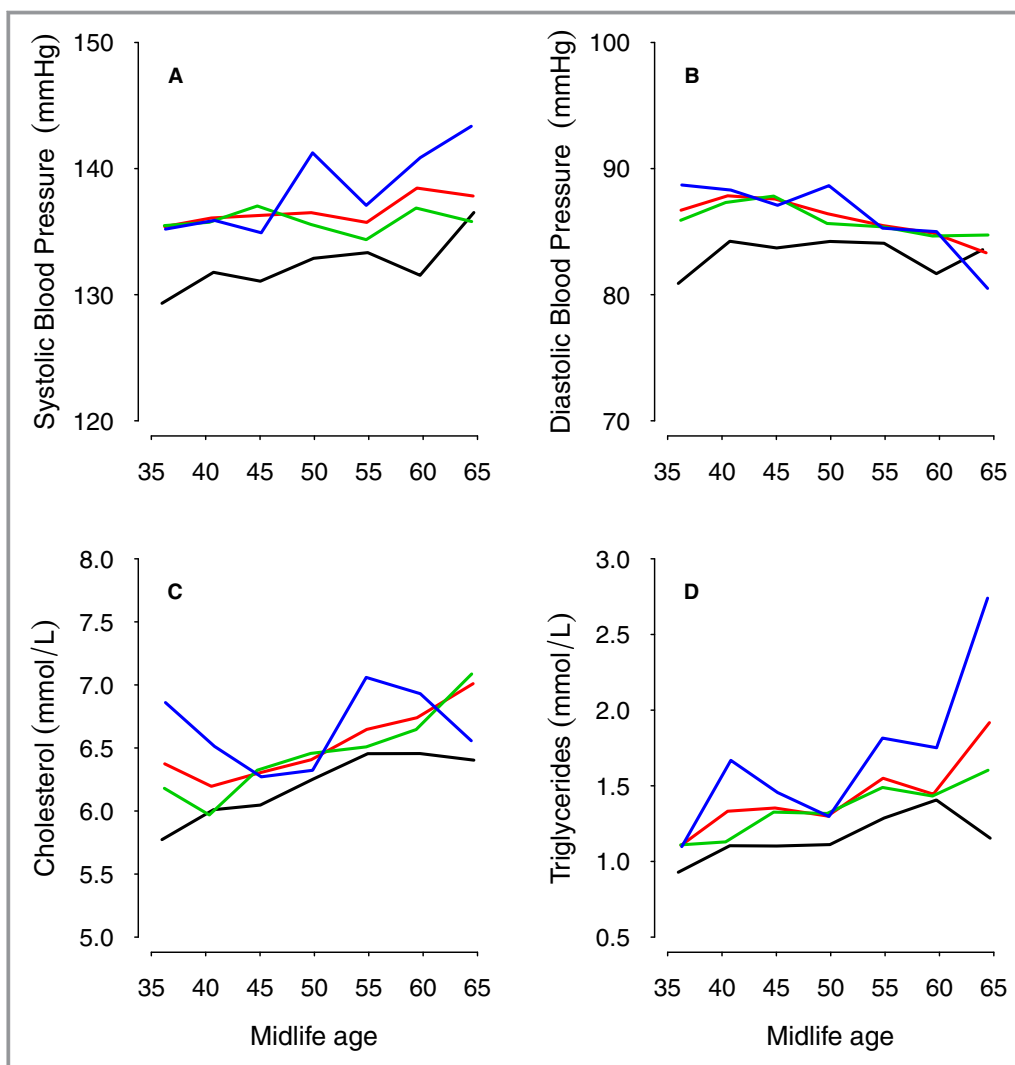


Figure. Five-year trends in midlife systolic (A) and diastolic (B) blood pressure, cholesterol (C), and triglycerides (D) with increasing age related to all MI and recognized and unrecognized MI (red line=all MI; blue line=recognized MI; green line=unrecognized MI; black line=no MI). MI indicates myocardial infarction.

terms of pathophysiologic mechanisms cannot be addressed in this study.

There are a number of limitations to this study. The modified Framingham risk score does not include measures of high-density lipoprotein cholesterol, and yet is still associated with later RMI and UMI. Also, the subjects are survivors still alive 31 years after the Reykjavik study. The prevalence of RMI versus UMI may alter with time, and so the relation of risk factors such as diabetes or smoking to a lethal disease could be underestimated (ie, survivor bias). MI itself can alter BP or cholesterol through pathophysiologic change, or prescription of drugs or diet, but the baseline midlife Reykjavik data are unlikely to have this limitation because the mean age was 48 years and probably before onset of MI in most cases. In the 1970s and 1980s, cardiovascular risk factor management was not as well defined as in current practice guidelines, which have lower thresholds for intervention for prehyperten-

sion and hypercholesterolemia.^{50,52,58} In the Reykjavik study, the baseline mean systolic and diastolic BPs at midlife were in the prehypertension range and higher than mean BPs reported in a recent National Health and Nutrition Examination Survey.⁵⁹

In this Icelandic cohort, atherosclerotic risk factors at midlife are associated with both UMI and RMI detected by CMR 31 years later. Among modifiable midlife risk factors studied, systolic BP was the most significant factor associated with UMI, although the impact of other important risk factors such as diabetes could not be addressed in this report. The paper highlights the finding that even minor elevations of mean levels of cardiovascular risk factors are associated with later RMI and UMI. From a public health perspective, it may be useful to test whether outcomes improve with early aggressive risk factor modification and use of CMR to detect UMI in asymptomatic high-risk populations.

Table 5. Association of Serial Midlife Risk Factors and Both Recognized and Unrecognized Myocardial Infarction Assessed by CMR in Later Life

Risk Factors Comparing MI vs No MI	Model I*		Model II†	
	β (SE)	P Value	β (SE)	P Value
Serial systolic blood pressure, mm Hg‡				
All MI vs no MI	3.20 (1.11)	0.004	3.21 (1.08)	0.003
Unrecognized MI	2.76 (1.31)	0.04	2.69 (1.28)	0.04
Recognized MI	4.03 (1.64)	0.01	4.12 (1.60)	0.010
Serial diastolic blood pressure, mm Hg‡				
All MI vs no MI	1.50 (0.63)	0.02	1.50 (0.62)	0.02
Unrecognized MI	1.18 (0.73)	0.11	1.18 (0.73)	0.11
Recognized MI	2.05 (0.94)	0.03	2.05 (0.91)	0.03
Serial cholesterol, mmol/L				
All MI vs no MI	0.25 (0.08)	0.001	0.25 (0.08)	0.001
Unrecognized MI	0.14 (0.09)	0.11	0.14 (0.09)	0.11
Recognized MI	0.43 (0.11)	0.0001	0.43 (0.11)	0.0001
Serial triglycerides, mmol/L§				
All MI vs no MI	0.15 (0.05)	0.002	0.15 (0.05)	0.002
Unrecognized MI	0.07 (0.06)	0.25	0.07 (0.06)	0.24
Recognized MI	0.31 (0.07)	<0.0001	0.30 (0.06)	<0.0001
Serial glucose				
All MI vs no MI	0.61 (0.58)	0.60	0.60 (0.58)	0.30
Unrecognized MI	0.48 (0.69)	0.48	0.43 (0.69)	0.53
Recognized MI	0.82 (0.85)	0.33	0.88 (0.84)	0.30
Serial body mass index, kg/m ²				
All MI vs no MI	0.13 (0.25)	0.60	0.15 (0.25)	0.54
Unrecognized MI	0.33 (0.30)	0.30	0.36 (0.29)	0.23
Recognized MI	−0.22 (0.38)	0.38	−0.20 (0.37)	0.60
Midlife physical activity				
All MI vs no MI	−0.10 (0.06)	0.11	0.09 (0.06)	0.17
Unrecognized MI	−0.00 (0.08)	0.96	0.01 (0.08)	0.85
Recognized MI	−0.26 (0.09)	0.006	−0.25 (0.09)	0.007

CMR indicates cardiac magnetic resonance imaging; β (SE), coefficient (standard error); MI, myocardial infarction.

*Model 1, mixed model adjusted for midlife age, late-life age, and sex.

†Model 2, mixed model adjusted for midlife age, late-life age, sex, midlife smoking, midlife antihypertensive medication, and midlife serum glucose.

‡Adjusted for antihypertensive medications.

§Adjusted for cholesterol.

||Physical activity: 1=never, 2=rarely, 3=occasionally, 4=moderate, 5=high.

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