

Prevalence of Unrecognized Myocardial Infarction Detected With Magnetic Resonance Imaging and its Relationship to Cerebral Ischemic Lesions in Both Sexes

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- Objectives** The purpose of this study was to investigate the prevalence of unrecognized myocardial infarction (UMI) detected with magnetic resonance imaging (MRI) and whether it is related to cerebral ischemic lesions on MRI in an elderly population-based cohort.
- Background** There is a correlation between stroke and recognized myocardial infarction (RMI) and between stroke and UMI detected with electrocardiography, whereas the prevalence of stroke in subjects with MRI-detected UMI is unknown.
- Methods** Cerebral MRI and cardiac late-enhancement MRI were performed on 394 randomly selected 75-year-old subjects (188 women, 206 men). Images were assessed for cerebral ischemic lesions and myocardial infarction (MI) scars. Medical records were scrutinized. Subjects with MI scars, with or without a hospital diagnosis of MI, were classified as RMI or UMI, respectively.
- Results** UMIs were found in 120 subjects (30%) and RMIs in 21 (5%). The prevalence of UMIs ($p = 0.004$) and RMIs ($p = 0.02$) was greater in men than in women. Men with RMI displayed an increased prevalence of cortical and lacunar cerebral infarctions, whereas women with UMI more frequently had cortical cerebral infarctions ($p = 0.003$).
- Conclusions** MI scars are more frequent in men than in women at 75 years of age. The prevalence of RMI is related to that of cerebral infarctions. (J Am Coll Cardiol 2011;58:1372–7) © 2011 by the American College of Cardiology Foundation

There is an established correlation between cerebral and myocardial ischemic lesions (1). The risk of experiencing a clinically recognized myocardial infarction (RMI) is increased in patients with transient ischemic attacks and ischemic stroke (1), and the risk of ischemic stroke is increased after an RMI (2). RMI risk is also increased in patients with lacunar stroke (3) and cerebral white matter lesions (particularly periventricular lesions) (4). General risk factors for stroke and RMI are similar, and both are considered to be manifestations of atherosclerotic disease (5).

The prevalence of clinically unrecognized myocardial infarction (UMI) has formerly been estimated with electrocardiography (ECG) (6,7), and men with ECG-detected UMI have an increased risk of stroke (8) and dementia (9). However, late-enhancement magnetic resonance imaging (LE-MRI) detects more UMIs than ECG (10), and subjects with magnetic resonance imaging (MRI)-detected UMI constitute another group, comprising both sexes, whose prevalence of stroke has not been investigated before. The pathogenesis of MRI-detected UMIs is unknown.

The aim of this study was to investigate the prevalence of MRI-detected UMI and whether it is related to cerebral ischemic lesions on MRI in an elderly population-based cohort.

Methods

Study population. After approval from the ethics committee, cardiac and cerebral MRI was performed on an unselected subsample from the PIVUS (Prospective Investiga-

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tion of the Vasculature in Uppsala Seniors) study (11). Eligible for the PIVUS study were all subjects aged 70 years and residing in the municipality of Uppsala, Sweden. The subjects were chosen in a random manner from the register of municipality inhabitants, and 2,025 subjects were invited to participate within weeks of their 70th birthday; 1,016 agreed to participate in that study. Five years later, 52 subjects from the original cohort had died. The remaining 964 were invited to participate in the present study; 826 agreed and gave written informed consent.

The estimated glomerular filtration rate was established in randomly selected subjects from this cohort, and 411 subjects with an estimated glomerular filtration rate >30 were invited to undergo cerebral and LE-MRI. Complete magnetic resonance (MR) examinations were performed for 394 subjects (188 women and 206 men).

Image acquisition. Imaging was performed on a 1.5-T MRI system (Gyrosan Intera, Philips Medical Systems, Best, the Netherlands) with a 25-mT/m gradient system.

MRI of the brain was performed using a quadrature head coil (receive only). The protocol included axial proton density and T2-weighted turbo spin echo images (TR 3000 ms, TE 21, and 100 ms, echo train length 16, pixel size 0.94×0.94 mm, slice thickness 3 mm), sagittal 3-dimensional T1-weighted gradient echo images (TR 8.6 ms, TE 4 ms, slice thickness 1.2 mm, pixel size 0.94×0.94 mm). After injection of 40 ml gadolinium-diethylenetriamine penta-acetic acid-bismethylamide (OmniscanTM, GE Healthcare, Oslo, Norway), an axial T1-weighted spin echo sequence was obtained (TR 567 ms, TE 11 ms, slice thickness 5 mm, pixel size 0.45×0.45 mm).

For cardiac imaging, the standard SENSE cardiac coil was used in the supine position and retrospectively gated vector ECG was used for cardiac triggering. Approximately 20 to 40 min after contrast injection (see previous text), late-enhancement images were acquired using a 3-dimensional inversion recovery gradient echo sequence covering the entire heart in short and long axis views. The acquired slice thickness was 10 mm with a resolution of 1.56×2.81 mm². The inversion time was individually adjusted to null viable myocardium for every subject.

Image analysis. For assessment of the images, a picture archiving and communication system workstation (Carestream PACS, Carestream Health Inc., Rochester, New York) was used.

The cerebral MR images were assessed by a neuroradiologist who was blinded to information on any previous disease and to the cardiac MRI findings. White matter changes, lacunar infarcts (measuring 3 to 15 mm), and cortical infarcts were assessed. The cerebral white matter lesions were graded regarding the severity of periventricular hyperintense white matter lesions and deep white matter hyperintense lesions according to the visual Fazekas scale (12). The subjects were also subdivided into 3 white matter lesion severity groups as in the LADIS (Leukoaraiosis and Disability) study (13).

Cardiac LE-MRI was assessed by a radiologist who was blinded to information on any previous disease and to the cerebral MRI findings. Left ventricular myocardium nulled by the inversion pulse was visually assessed as viable, whereas left ventricular myocardium showing late enhancement (i.e., hyperintense myocardium) was classified as nonviable. To classify myocardium as nonviable, late enhancement had to be visible in short and long axis images. Late enhancement that involved the subendocardial layer was considered to represent an MI scar (14,15) and is hereafter referred to by that term.

Subject data. The participants completed a questionnaire about their medical and drug histories, and their blood pressure was measured. A venous blood sample was taken in the morning after an overnight fast. No medication or smoking was allowed after midnight. Fasting blood glucose, low-density and high-density lipoprotein cholesterol levels were measured using standard techniques.

The medical records of subjects displaying MI scars were scrutinized for the diagnosis of MI by a physician blinded to the MRI findings. Subjects with a hospital diagnosis of MI, before the MR examination, were considered to have had a clinical MI and are hereafter referred to by that term.

Three groups were formed based on the late enhancement findings and the data from medical records: 1 group of subjects without MI scars (no MI), 1 group of subjects with an MI scar but no clinical MI (i.e., a UMI), and 1 group of subjects with both an MI scar and a clinical MI (i.e., an RMI).

Statistical analysis. StatView version 5.0.1 (SAS Institute, Cary, North Carolina) was used for statistical analyses. The Fisher exact test was used to estimate differences between groups. Logistic regression was performed to test interactions between sex and the 2 MI types and to test interactions between cardiovascular risk factors and the 2 MI types. The significance level was set at 0.05 in all analyses.

Results

Basic characteristics and major cardiovascular risk factors of women and men are displayed in Table 1. There were significant differences in blood pressure, heart rate, and serum lipid levels. In a logistic regression model, UMI remained significantly associated with cortical infarcts for women for all significantly different parameters, and RMI remained significantly associated with cortical and lacunar infarcts for men for all parameters except for the association between low-density lipoprotein cholesterol and lacunar infarcts, which lost somewhat in significance ($p = 0.059$).

Abbreviations and Acronyms

ECG = electrocardiography

LE-MRI = late-enhancement magnetic resonance imaging

MI = myocardial infarction

MR = magnetic resonance

MRI = magnetic resonance imaging

RMI = recognized myocardial infarction

UMI = unrecognized myocardial infarction

Table 1 Basic Characteristics and Major Cardiovascular Risk Factors in Women and Men

	Study Population (N = 394)		
	Women (n = 188)	Difference	Men (n = 206)
Body mass index, g/m ²	26.7 ± 4.6	NS	26.9 ± 3.8
Systolic blood pressure, mm Hg	150.4 ± 19	*	145.7 ± 18
Diastolic blood pressure, mm Hg	74.5 ± 8.9	*	77.3 ± 11
Heart rate, beats/min	66.2 ± 11	*	62.6 ± 11
Serum cholesterol, mmol/l	5.7 ± 1.0	*	5.1 ± 1.1
LDL cholesterol, mmol/l	3.5 ± 0.9	*	3.2 ± 1.0
HDL cholesterol, mmol/l	1.7 ± 0.4	*	1.3 ± 0.4
Serum triglycerides, mmol/l	1.3 ± 0.6	NS	1.3 ± 0.7
Fasting blood glucose, mmol/l	5.1 ± 1.4	NS	5.4 ± 1.4
Hypertension	45.5	NS	50.7
Diabetes	10.6	NS	9.7
Current smoking	4.3	NS	6.9

Values are mean ± SD or %.*Statistically significant difference (i.e., p < 0.05). HDL = high-density lipoprotein; LDL = low-density lipoprotein.

MI scars were found in 141 of the 394 subjects (36%); 49 of these were women and 92 were men. The subjects with RMI constituted 5% (21 of 394) of the entire cohort, 3% (5 of 188) of women, and 8% (16 of 206) of men, whereas the subjects with UMI constituted 30% (120 of 394) of the entire cohort, 23% (44 of 188) of women, and 37% (76 of 206) of men (Fig. 1). Women constituted 24% (5 of 21) of the RMI group, 37% (44 of 120) of the UMI group, and 55% (139 of 253) of the group without MI scars. The prevalence of UMIs (p = 0.004) and RMIs (p = 0.02) was greater in men than in women.

Cortical cerebral infarctions were found in 23 of the 394 subjects (6%); 7 of these were women and 16 were men. Lacunar cerebral infarctions (3 to 15 mm) were found in 87 of the 394 subjects (22%); 35 of these were women and 52 were men. Using the visual Fazekas scale (12), periventricular hyperintense white matter lesions grades 2 to 3 were found in 185 of the 394 subjects (47%) (92 women, 93 men) and deep white matter hypertense lesions grades 2 to 3 in 181 of the 394 (46%) (83 women, 98 men). When using the criteria described in the LADIS study (13), grade 2 to 3 changes were found in 177 of the 394 subjects (45%) (83 women, 94 men). There was no significant difference between the sexes in the prevalence of cerebral lesions (Table 2).

Subjects with RMI displayed an increased prevalence of cortical cerebral infarctions compared with subjects with UMI (p = 0.004) and subjects without MI scars (p < 0.0001) (Fig. 2). Subjects with RMI also displayed an increased prevalence of lacunar cerebral infarctions compared with subjects with UMI (p = 0.012) and subjects without MI scars (p = 0.004) (Fig. 3). The prevalence of cerebral white matter lesions did not differ between the groups.

Sex-specific analysis was performed, resulting in similar differences in men as in the entire cohort (Figs. 4B and 5B).

In women, the prevalence of cortical infarcts was significantly different in subjects with UMI (5 of 44 [11%] had cortical infarcts) compared with subjects without MI scars (2 of 143 [1%] had cortical infarcts) (p = 0.003), whereas there were no women with cortical infarcts in the RMI group (Fig. 4A). There were no differences in the prevalence of lacunar infarcts in women among the 3 groups (Fig. 5A).

In a logistic regression model, the interaction term sex × UMI was significant for women in predicting cortical infarcts (p = 0.01) and the interaction term sex × RMI was significant for men in predicting cortical (p = 0.0004) and lacunar (p = 0.01) infarcts.

Discussion

The observed prevalence of MRI-detected UMI was higher in this cohort of community-living 75-year-old subjects (30%) than in community-living 70-year-old subjects (20%) (10). It was only slightly higher than in generally younger patients with end-stage renal disease (25%) (16) or those with suspected coronary artery disease (27%) (17). These differences may be attributed to the process of normal aging and its associated increased morbidity. The prevalence of RMI in women and men is consistent with that in other studies (18).

It is well-known that men have about twice the total incidence of RMI compared with women (19), which is confirmed by the results of the present study. Moreover, it was observed that UMIs were more frequent in men than in women. This is somewhat in contrast with the observation at 70 years of age, where women constituted 45% of the UMI group and 18% of the RMI group (10). At 75 years of age, they constitute 37% of the UMI group and 24% of the

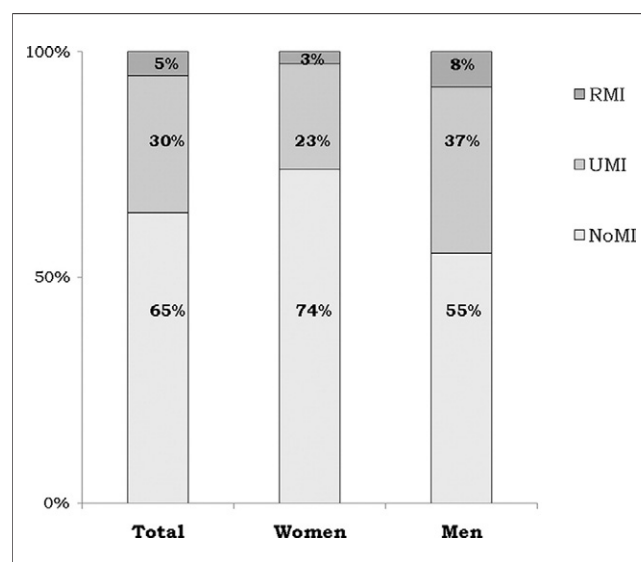


Figure 1 Distribution of Myocardial Infarction Scars

The distribution of recognized myocardial infarction (RMI) and unrecognized myocardial infarction (UMI) on magnetic resonance imaging in the entire cohort (total) and in women and men separately. NoMI = without myocardial infarction scars.

Table 2 Prevalence of Cerebral Ischemic Lesions in Women and Men With or Without Myocardial Infarction Scars on Cardiac Magnetic Resonance Imaging

	NoMI		UMI		RMI	
	Women (n = 139)	Men (n = 114)	Women (n = 44)	Men (n = 76)	Women (n = 5)	Men (n = 16)
Cortical infarcts	2	6	5	4	0	6
Lacunar infarcts	24	27	10	16	1	9
PVHs (Fazekas)	68	48	23	37	1	8
DWMHs (Fazekas)	62	51	20	36	1	11
White matter lesions (LADIS)	62	48	20	36	1	10

DWMH = deep white matter hyperintense lesions according to the visual Fazekas scale; LADIS = Leukoaraiosis and Disability study; NoMI = no myocardial infarction scar on magnetic resonance imaging; PVH = periventricular hyperintense white matter lesions according to the visual Fazekas scale; RMI = recognized myocardial infarction; UMI = unrecognized myocardial infarction.

RMI group, suggesting that MIs in women are recognized to a larger extent at age 75 years than they were 5 years earlier. This corresponds to the Framingham study reporting that MIs in women are more likely to be unrecognized than MIs in men, but that this difference tends to diminish after menopause and to be eliminated around the seventh decade of life (19).

The association between UMIs and cortical infarcts in women and that between RMIs and cortical infarcts in men remained despite sex differences in blood pressure, heart rate, and serum lipid levels, whereas the association between RMIs and lacunar infarcts in men was slightly impaired. Hence, these associations are not to any large extent influenced by the investigated demographic and clinical variables.

The prevalence of cerebral infarctions in the present study is consistent with observations made in other population-based cohorts (20) and so is the prevalence of white matter changes (20–22). The observation that elderly subjects with RMI displayed an increased prevalence of cortical and

lacunar cerebral infarctions was more or less expected because these are all manifestations of atherosclerotic disease (5). This correlation has also been observed by others (23,24). However, sex-specific analysis of our data indicated that this may only be true in men, which might be explained by the fact that there were fewer women than there were men displaying MI scars.

In women, cortical cerebral infarctions were more frequent in subjects with UMI than in those without MI scars. Even though there were few subjects in these groups (5 of 44 in the UMI group and 2 of 139 in the no MI group), the difference is statistically significant, and this observation might indicate an increased risk of stroke for women with MRI-detected UMI. Others have reported an increased risk of stroke for men with ECG-detected UMI (8), but these are not the same UMIs (10) because the criteria defining UMIs differ substantially between the methods (MRI defines a UMI as contrast-enhanced nonviable myocardium, whereas ECG defines a UMI by the existence of a pathological Q-wave). It is probable that MRI is more sensitive

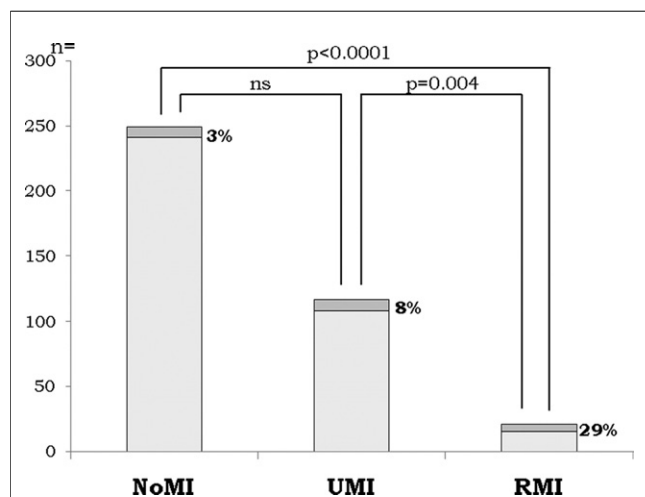


Figure 2 Prevalence of Cortical Infarcts

The prevalence of cortical cerebral infarctions on magnetic resonance imaging in NoMI, UMI, and RMI subjects. p values are displayed where there are statistically significant differences. Abbreviations as in Figure 1.

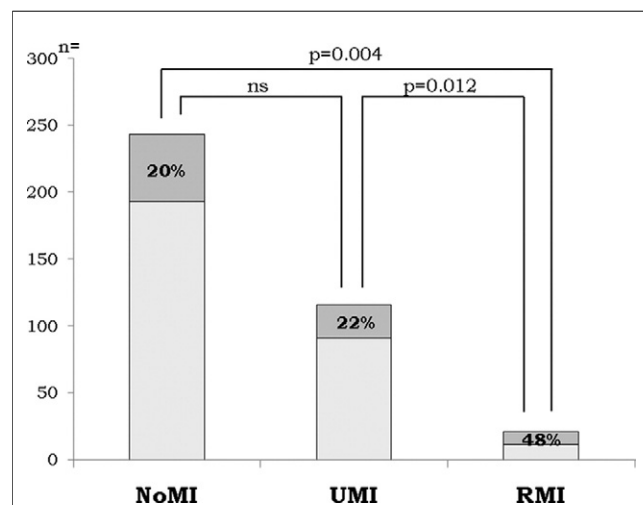


Figure 3 Prevalence of Lacunar Infarcts

The prevalence of lacunar cerebral infarctions on magnetic resonance imaging in NoMI, UMI, and RMI subjects. p values are displayed where there are statistically significant differences. Abbreviations as in Figure 1.

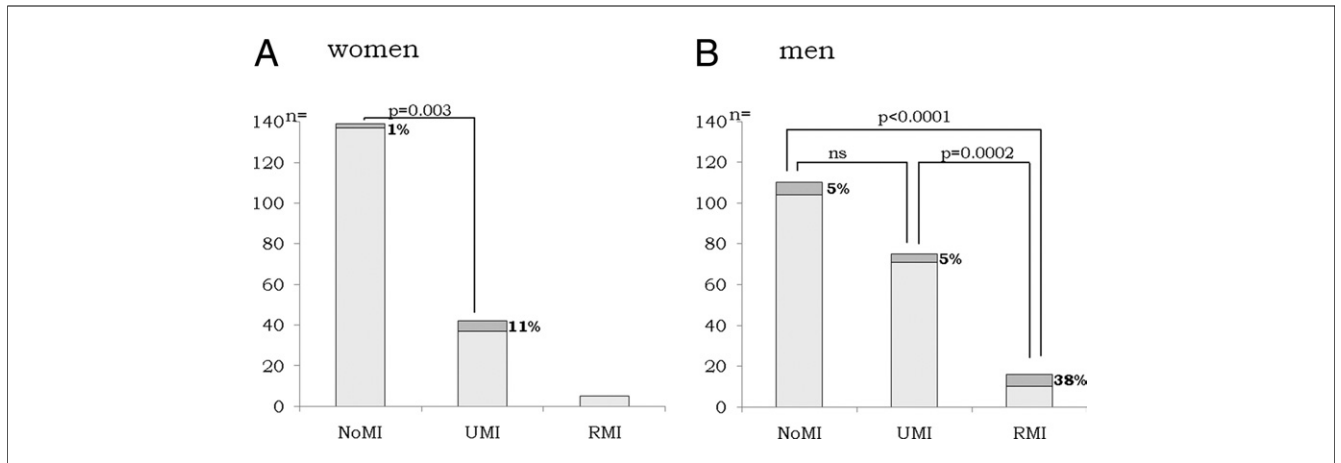


Figure 4 Sex-Specific Prevalence of Cortical Infarcts

The prevalence of cortical cerebral infarctions on magnetic resonance imaging displayed separately for women (A) and men (B) NoMI, UMI, and RMI subjects. p values are displayed where there are statistically significant differences. Abbreviations as in Figure 1.

than ECG in detecting UMIs; for example, the prevalence of MRI-detected UMI is 3-fold higher than ECG-detected UMI in patients with suspected coronary artery disease (17).

MRI-detected UMIs are not associated with manifestations of significant atherosclerosis on whole-body MR angiography nor with increased carotid intima-media thickness, elevated plasma levels of high-sensitivity C-reactive protein, or traditional risk factors of coronary heart disease (25). This may be interpreted in 2 different ways: either these UMIs have a different pathogenesis from that of RMIs or they have the same pathogenesis but present themselves at an earlier stage (25). The lack of association between ischemic cerebral lesions and UMIs in the entire cohort of the present study supports the former interpretation.

However, cortical cerebral infarcts are considered to be a manifestation of atherosclerosis (5), but the pathogenesis of lacunar strokes has been suggested to differ from the

atherothrombotic process (26). Thus, a hypothetical association between UMIs and lacunar infarcts would further have supported the interpretation that UMIs are *not* caused by atherosclerosis, whereas an association between UMIs and cortical infarcts would have suggested that UMIs *are* caused by atherosclerosis.

Because an association between UMIs and cortical infarcts was observed in women, their UMIs might be caused by atherosclerosis. This could imply that MRI-detected UMIs have a different pathogenesis in women than they have in men. However, it may be more likely that the vascular vulnerability differs between women and men, so that atherosclerosis would manifest itself earlier in cerebral vessels in women and earlier in cardiac vessels in men. It is known that men with coronary artery disease have a greater atherosclerotic plaque burden than women with coronary artery disease (27). There might be protective factors influ-

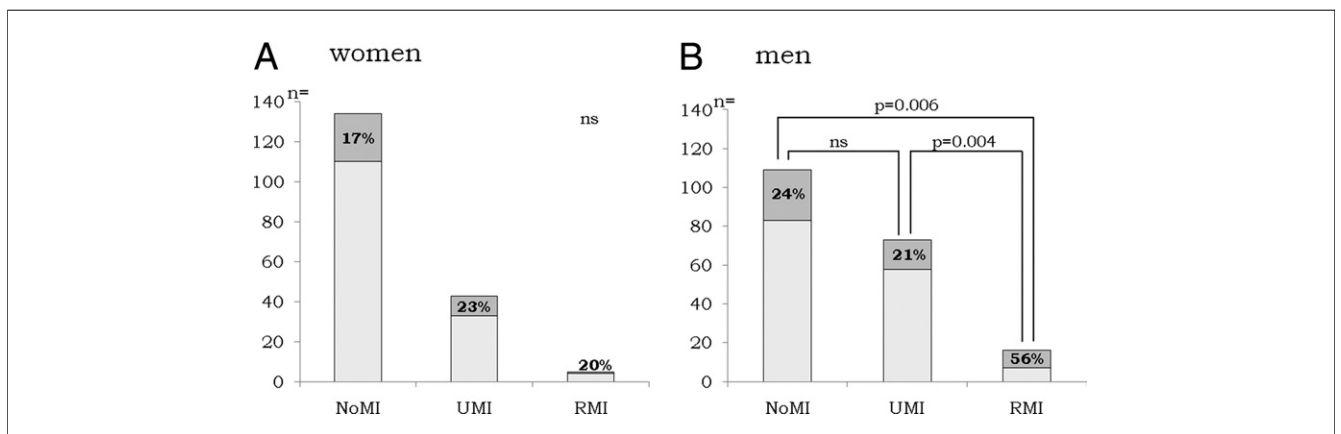


Figure 5 Sex-Specific Prevalence of Lacunar Infarcts

The prevalence of lacunar cerebral infarctions on magnetic resonance imaging displayed separately for women (A) and men (B) NoMI, UMI, and RMI subjects. p values are displayed where there are statistically significant differences. Abbreviations as in Figure 1.

encing women's cerebral and cardiac vessels equally, but only influencing men's cerebral vessels and not their cardiac vessels, or there might be a male-specific risk factor that influences only cardiac vessels.

Study limitations. The present study was limited by the fact that the compared sex-stratified subgroups, and consequently the endpoint rates, were very small, rendering any statistical difference uncertain. This also omits the possibility to correct for biases statistically because multivariate analyses are not applicable. Thus, the association between cortical infarcts and UMI that was observed in women is rather weak and may be regarded as a preliminary result.

Conclusions

The prevalence of MRI-detected UMI seems to increase with age, and MI scars are more frequent in men than in women at 75 years of age. MIs in women tend to evolve from being unrecognized to becoming recognized at an older age. Subjects with RMI display an increased prevalence of cortical and lacunar cerebral infarctions. This might only apply to men, whereas women with UMI display an increased prevalence of cortical cerebral infarctions. Further studies are needed to clarify sex-specific morbidity correlations and risks.

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