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Population distribution of traditional and the emerging cardiovascular risk factors carotid plaque and IMT: the REFINE-Reykjavik study with comparison with the Tromsø study

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ABSTRACT

Objectives Population statistics for carotid plaque and cardiovascular risk factors reported in scientific journals are usually presented as averages for the population or age and sex adjusted, rather than sex and age groups. Important population differences about atherosclerosis and cardiovascular risk factors may thus be missed. We compare the distribution of cardiovascular risk factors, carotids plaque and carotid intima-media thickness (CIMT) in two population-based studies.

Methods Carotid artery atherosclerotic plaque prevalence and risk factors levels for cardiovascular disease by sex in 5-year age groups from the Risk Evaluation For Infarct Estimates Reykjavik study (REFINE-Reykjavik study) were compared with data from the Tromsø 6 study.

Results The threshold of carotid plaque presence in the Tromsø 6 study fell between minimal and moderate plaque defined in the REFINE-Reykjavik study reflecting carotid plaque prevalence. The prevalence of minimal carotid plaque in the REFINE-Reykjavik study was 47% in men (40–69 years old) and 38% in women and 11% in men and 7% in women of moderate plaque. The prevalence of any plaque in the Tromsø 6 study was 35% in men and 27% in women. The mean (CIMT) was similar in the studies. In the Tromsø 6 study mean systolic blood pressure was 8 mm Hg higher in men and 10 mm Hg higher in women, mean low-density lipoprotein was 0.5 mmol/L higher in men and 0.3 mmol/L higher in women and the prevalence of smoking was 4% higher in men and 9% higher in women. However, body mass index was 0.8 kg/m^2 higher in men and 0.9 kg/m^2 in women in the REFINE-Reykjavik study.

Conclusion Comparison between Iceland and Norway revealed differences in the prevalence of carotid plaque, which was assumed to be due to different definition of plaque. However, clinically significant differences in conventional cardiovascular risk factors were seen. This underscores the importance of detailed comparison of population data across different populations.

Strengths and limitations of this study

- ► The strength of this study is the random population design of both the Risk Evaluation For Infarct Estimates Reykjavik study (REFINE-Reykjavik study) and the Tromsø 6 study.
- ► The rigid protocols of the two studies regarding data gathering and quality control and that the studies were conducted at similar time interval is also strength.
- ► The main limitation of the study are differences in carotid ultrasound protocols between the REFINE-Reykjavik study and Tromsø 6 study. The study was done on Caucasian participants only.

INTRODUCTION

The value of comparing risk factors of cardiovascular disease between populations is undisputed. The Seven Countries Study and the WHO-led Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Project are examples of studies that have monitored changes in risk factors and compared diets and lifestyles between countries. These studies contributed to knowledge, which led to changes in risk factor levels and the drop seen in the prevalence of coronary heart disease in the last decades of the 20th century.[1 2] However, detailed information on the presence of atherosclerotic plaque in the carotid arteries across different populations is not readily available in the current literature. Population statistics for carotid plaque and for cardiovascular risk factors reported in scientific journals are usually presented as an average for the population or adjusted for age and sex, rather than being reported by different sex and age groups. Thereby, significant sex and age interaction in the

development in atherosclerosis and/or in cardiovascular risk factors can be missed in comparison across different populations based on published data. For carotid plaque, which is one of the best studied markers of subclinical atherosclerosis, different definitions of carotid plaque between studies also complicate the comparison.

We now publish results from the first phase of the Risk Evaluation For Infarct Estimates Reykjavik study (REFINE-Reykjavik study), which started in December 2005 and completed in March 2011. The REFINE-Reykjavik study is a prospective cohort study on risk factors and aetiology of atherosclerotic disease in the population of the Reykjavik area in Iceland. The study was performed on a large number (6661) of individuals (25–69 years of age) with ultrasound of the carotids and other measurements of both traditional risk factors and new risk factors for cardiovascular disease. The aim of REFINE-Reykjavik study was to demonstrate what characterises individuals who develop atherosclerosis and to understand if carotid plaque or other factors measured in the study increase the accuracy of risk estimates for cardiovascular disease.

The population distribution of cardiovascular risk factors and the prevalence of atherosclerotic plaque in the common carotid arteries are presented in adults living in the greater Reykjavik area according to age groups and sex. We report the data in this detailed manner in order to make comparisons with other studies easier and more accessible. We also make direct comparison between results from the REFINE-Reykjavik study and the Tromsø 6 study and discuss the results in context with available outcomes from other population studies in Europe and USA. The two population studies, the REFINE-Reykjavik study and the Tromsø 6 study, were conducted within the similar time interval (REFINE-Reykjavik study: 2006–2011; Tromsø 6: 2007–2008), which included both genders and both included middle-aged participants, mostly of Scandinavian origin and are therefore highly comparable.

METHODS

Study population

The cohort in the first phase of the REFINE-Reykjavik study was a random sample of 9.480 men and women born in 1935–1985, living in Reykjavik in November in the year 2005 and with Icelandic citizenship. The cohort was divided into 5-year age groups from 25 to 69 years. The age distribution was designed to over-represent middle-aged individuals in order to concentrate the power of the study on the age span where development of atherosclerosis was to be most expected. In the age groups 25–34 years, the number of individuals in each age group was 600, in the age groups from 35–64, the number was 1200 in each group and in the age group 65–69 years, the number of individuals was 480. The cohort in the REFINE-Reykjavik study was drawn from the same geographic area as the well-established Reykjavik study. The cohort in the Reykjavik study included individuals born in 1907–1935.[3] The birth year bracket in the REFINE-Reykjavik study (1935–1985) is therefore in continuation of the Reykjavik study.

The cohort in REFINE-Reykjavik study is homogenous with the vast majority being of Scandinavian origin. Icelanders are genetically similar to other northern European countries,[4] and risk of coronary heart disease and the contribution of the conventional risk factors to this risk is similar.[5] In the final survey of the WHO MONICA Project conducted in 1992, of the 38 population investigated for coronary event rate in men, the Icelandic population was approximately in the middle. Twenty populations had higher coronary event rate, and 17 populations had lower coronary event rate than the Icelandic population.[6] For comparison of both conventional risk factors for coronary heart disease, prevalence of carotid plaque and the level of CIMT in the population, data from Tromsø 6 study were used.

The Tromsø study is an ongoing population-based cohort study in the municipality of Tromsø, Northern Norway, with a population of 72 000 inhabitants. The Tromsø 6 study was conducted in the years 2007–2008. The age span was 40–87 years. Invited to Tromsø 6 first visit were all residents aged 40–42 years and 60–87 years (n=12 578), a 10% random sample of individuals aged 30–39 years (n=1056), a 40% random sample of individuals aged 43–59 years (n=5787) and subjects who had attended the second visit of Tromsø 4, if not already included in the three groups above (n=341). The attendance rate was 66%.

Detailed description on recruitment methods, use of medication and supplements, clinic examination, blood analyses, quality control of the ultrasound of the carotid arteries in the REFINE-Reykjavik study is shown in online supplementary text 1, and description of Tromsø 6 is available in online supplementary text 2.

Ultrasound of the carotid arteries

In the REFINE-Reykjavik study, the ultrasound of the carotid arteries was performed using a standardised scanning and analysis protocol for quantitative assessment of the common carotid intima-media thickness (IMT) and arterial stiffness. The protocol also included scans for semiquantitative assessment of plaque presence/absence and plaque severity. The protocol was developed by experts from the Vascular Imaging Center, Julius Center for Health Care and Primary Care in the University of Utrecht in the Netherlands (MLB). The technicians who performed the ultrasound studies were trained by the same experts that developed the protocol.

The carotid arteries on both sides were imaged from four different interrogation angles with 30° increments using a Sequoia C256, Acuson ultrasound system (Siemens Medical Systems, Erlangen, Germany) with an 8.0 MHz transducer. To standardise and control the interrogation angles, the Meijers Carotid Arc was used.[7] The IMT measurements were quantified on a predefined segment in near and far wall of the carotid common arteries[8] using the Artery Measurement Software (AMS) II V.1.131.

Outcome parameters

Common carotid IMT

B-mode images of the IMT are acquired for the predefined 10 mm segment of each common carotid artery[8] (right and left) at defined interrogation angles using Meijers Arc. Standard images are obtained from four angles at each site. The mean IMT of the near (shallower) and far (deeper) walls are determined from a single image at each interrogation angle for both the right and left common carotid arteries CCA. The average of all these IMT values comprised the mean IMT outcome parameter. The maximum IMT corresponded to the highest measured IMT value at the four angles.

Atherosclerotic plaque in the carotid bifurcation and internal carotid artery

Of the left and right carotid bifurcation and internal carotid artery, the presence of atherosclerotic lesions is measured on line, that is, during the ultrasound examination. The most severe lesion per segment is assessed in a semiquantitative manner. The plaque image interpretation is based on the following four categories:

1. None: complete absence of plaque, IMT thickening may be observed.
2. Minimal: small isolated thickening, unifocal or multifocal, often with calcification approximately two times the adjacent normal IMT.
3. Moderate: clear, reasonably easy to visualise plaque with or without calcification. May be located on both near and far wall in the segment causing some diameter reduction.
4. Severe: significant plaque formation very easy to image with or without calcifications and visualised on several different scan projections in near and far wall causing clear diameter reduction.

Images of observed plaques were stored.

In the Tromsø 6 study, high-resolution B-mode ultrasonography was performed with GE Vivid 7 duplex scanners with linear 12 MHz transducers. The ultrasonographers were blinded to laboratory and clinical data. Subjects were examined in the supine position with the head slightly tilted to the left side. The sonographers were instructed to view the arteries from all possible angles, in order to find the optimal view for visualisation of plaque and IMT in each subject. No fixed angle of insonation was used. Measurements of plaque and IMT were analysed offline with the semiautomated AMS software. A plaque was defined as a localised protrusion into the vessel lumen of more than 50% thickening compared with the adjacent IMT. Six locations were scanned for the presence of plaques, the far and near walls of the right common carotid artery, bifurcation and internal carotid artery. ECG-triggered uptakes of IMT were obtained from the distal 10 mm segment of the far and near wall of the common carotid artery and of the proximal 10 mm segment of the far wall of the carotid bifurcation. Plaques were included in the IMT measurements if present in the predefined location of interest. The mean IMT from the three preselected images was calculated for each location, and the average of the mean IMT from the three locations was used in the analyses. The interobserver and intraobserver and interequipment reproducibility of IMT and plaque measurements was acceptable.[9–11]

STATISTICAL METHODS

Age-standardised means and proportions were presented and compared between the REFINE-Reykjavik and the Tromsø 6 study. The following risk factors were investigated: systolic blood pressure, low density lipoprotein, body mass index (BMI), prevalence of type 2 diabetes, cholesterol-lowering medications (statins), hypertension medication, smoking, self-reported history of coronary heart disease, IMT and plaque in the right carotids.

Age standardisation was done according to the direct method, using the standard population age structure as defined by the European Standard Population.[12] Statistical significance between study summary estimates was investigated using linear regression for continuous variables and logistic regression for categorical variables. Regressions were run separately for each sex and adjusted for age.

IMT and prevalence of plaque in right carotids was presented visually by sex, age groups and study. Blood pressure measurements in the REFINE-Reykjavik study were done using arterial tonometry,[13] whereas an electronic sphygmomanometer (Dinamap ProCare 300 monitor, GE Healthcare) was used in Tromsø 6 study. A set of approximately 400 available and concurrently measured sphygmomanometer readings in REFINE-Reykjavik study were compared with tonometry measurements using a linear mixed effects model, accounting for an inherent repeated measures aspect. Age-specific,sex-specific and method-specific predicted values were used to obtain a correction factor, which was applied to the tonometry measurements in REFINE, in an effort to make them comparable with the Tromsø 6 study measurements.

Statistical analysis was done using Stata V.14.1.[14]

RESULTS

Recruitment for the REFINE-Reykjavik study started in December 2005 and was completed in March 2011. The total number of individuals who participated in the study was 6661—3277 men and 3384 women. The recruitment rate was 73%. The sex ratio was 49% men and 51% women. The mean age was 49.8 years (SD 11.2 years), and the age range was 25–69 years.

The mean BMI for men was 27.7 (SD 4.3) kg/m^2 and 26.7 (SD 5.3) kg/m^2 for women. Mean BMI was above 25 kg/m^2 in both sexes, which is the upper limit of ideal weight according to WHO expert committee report.[15] BMI increased with increasing age (online supplement 3 table 1a).

Both systolic and diastolic blood pressures rose with age, but there was a decrease in the diastolic blood pressure

in the oldest age group (65–69 years old) in both sexes. Average systolic blood pressure in men was 125.5 mm Hg (SD 13.9) and 115.5 mm Hg (SD 13.7) for women, and average diastolic blood pressure was 70.7 mm Hg (SD 10.0) and 68.7 mm Hg (SD 9.0), respectively (online supplement 3 table 1a).

A steady increase in total cholesterol (TC), low-density lipoprotein (LDL) and triglycerides was observed in women with increasing age. In men, TC, LDL and TG peaked in middle age, decreasing again over the age of 60 years. HDL cholesterol increased with age in both sexes (online supplement 3 table 1b).

Family history of myocardial infarction increased with age and was somewhat higher in men than women (online supplement 3 table 2a). History of cardiovascular disease and history of coronary heart disease was rare in participants younger than 50 years old but increased sharply with age in men, and it was 22.9% and 20.4%, respectively, in 65–69 years old men (online supplement 3 table 2b). The increase was more gradually in women, history of cardiovascular disease and history of coronary heart disease was 6.0% and 4.3%, respectively, in 65–69 years old women (online supplement 3 table 2a).

The prevalence of diabetes type 2 in men on average was 6% and age adjusted was 4.3%. The prevalence is lower in women than in men or 3% and age adjusted 2.4%. The prevalence of diabetes increased with age in both sexes (online supplement 3 table 2b).

Hypertension was rare among young women (25–29 years), but 10% of young men had hypertension. With increasing age, the prevalence of hypertension increased sharply so that in the oldest age group (65–69 years), the majority of men (71%) and more than half of the women were hypertensive (online supplement 3 table 2b)

Use of blood pressure-lowering drugs and cholesterol-lowering drugs (statins) is shown in online supplement 3 table 2b. Drug treatment increased with age and was highest in the oldest age group. In the age group 65–69 years, 57.1% men and 51.4% women were on treatment against high blood pressure, and 33.8% of men and 18.4% of women were treated with statins (online supplement 3 table 2b).

Current smoking was highest in the age group 25–29 years in both men (28.8%) and women (27.4%). The prevalence of current smoking decreases with increasing age. On average, 23% of men and 22% of women smoked (online supplement 3 table 3a).

Overweight, defined as BMI ≥25, was very common in men (73%) and in women (56%), and obesity, defined as BMI ≥30, was seen in 25% of men and 22% of women (online supplement 3 table 3a).

About 14% of men and women had cholesterol levels above 6.2 mmol/L (online supplement 3 table 3b).

Physical activity was assessed by the following question in the health history questionnaire: 'In the past 12 months, how often did you participate in moderate or vigorous physical activity (Examples of moderate or vigorous physical activity include badminton. golf (walking), biking, swimming, heavy gardening, weight lifting, hiking/mountain climbing, fast walking/fast dancing/heavy housework, rowing, aerobics, jogging and running)'. About 60%–70% of men and women participated in at least moderate physical activity for 1–3 hours a week, and 30%–40% were active 4–7 hours a week. No clear difference in physical activity was seen between men and women or different age groups (online supplement 3 table 3b).

In online supplement 3 table 4a, mean common CIMT values are shown according to age and sex. The mean CIMT was 0.71 mm (SD 0.10) in men and 0.67 mm (SD 0.08) in women. CIMT increased steadily with increasing age in both sexes and was slightly higher in men than in women. For example, in the oldest age group (65–69 years), the mean CIMT was 0.91 mm (SD 1.3) in men but 0.85 (SD 0.11) mm in women. Results from the maximum IMT thickness are also shown in online supplement 3 table 4a. Maximum IMT values increased similarly with age, and the sex difference was similar.

The prevalence of carotid plaque increased with age in both sexes (online supplement 3 table 4b). The prevalence was somewhat higher in men than women at all ages although the sex difference was small. For example, 7.7% of men aged 50–54 years had moderate plaque compared with 5.3% of women. Severe plaque or semi-occlusion was never detected in the younger participants but was detected in 4.8% and 5.0% in the oldest women and men, respectively. In the youngest age group (25–29 years), 94.2% of men and 96.5% of the youngest women had no plaques, while this was seen in only 15.6% of the oldest men (65–69 years) and 21.6% of the oldest women (online supplement 3 table 4b).

Table 1 shows the characteristics of the REFINE-Reykjavik study and the Tromsø 6 study in men and women aged 40–69 years.

The systolic blood pressure was 8 mm Hg higher in men and 10 mm Hg higher in women in the Tromsø 6 study than the REFINE-Reykjavik study. Participants in REFINE-Reykjavik study were more often taking antihypertensive medication than in the Tromsø 6 study (30% vs 18% in men and 28% vs 17% in women). Calculated LDL cholesterol was somewhat higher in both men and women in the Tromsø 6 study than in REFINE-Reykjavik study (0.5 mmol/L in men and 0.3 mmol/L in women). The prevalence of statin use was similar in the two studies, although somewhat more men were taking statins in REFINE-Reykjavik study than Tromsø 6 study (16% vs 13%) but less women (7% vs 9%). Smoking was less prevalent in REFINE-Reykjavik study than the Tromsø 6 study in both sexes, but BMI was nearly one unit higher in the REFINE-Reykjavik study in both sexes. The prevalence of type 2 diabetes was similar in men in both studies (7.4%) but was lower in women in the REFINE-Reykjavik study (3.9% vs 4.9%). The mean far wall CIMT in men was 0.02 mm thicker in the Tromsø 6 study than the REFINE-Reykjavik study (p value <0.05) and 0.01 mm thicker in women (not significant) (table 1). The prevalence of minimal or more right

Table 1 Age standardised characteristic of participants in the REFINE-Reykjavik study and the Tromsø 6 study†

	Men aged 40–69 years			Women aged 40–69 years		
	REFINE-Reykjavik (n=2629)	Tromsø 6 (n=2214)	Difference	REFINE-Reykjavik (n=2719)	Tromsø 6 (n=2981)	Difference
Mean crude age (years) (SD)	54 (8.2)	59 (5.7)	−5	54 (8.2)	59 (6.1)	−5
Systolic BP‡ (mm Hg) (SD)	130 (15.5)	138 (17.7)	−8**	123 (15.5)	133 (21.4)	−10**
LDL (mmol/L) (SD)	3.3 (0.9)	3.8 (0.9)	−0.5**	3.3 (0.9)	3.6 (0.9)	−0.3**
BMI (kg/m^2) (SD)	28.4 (4.4)	27.6 (3.7)	0.8**	27.3 (5.3)	26.4 (4.7)	0.9**
CIMT§ mean far wall (mm) (SD)	0.77 (0.12)	0.79 (0.15)	−0.02*	0.72 (0.10)	0.73 (0.12)	−0.01
Current smoker, % (number)	21 (549)	25 (537)	−4**	20 (558)	29 (777)	−9
HTMED¶ users, % (number)	30 (776)	18 (532)	12**	28 (759)	17 (690)	11**
Statin users, % (number)	16 (410)	13 (401)	3*	7 (192)	9 (425)	−2*
Known heart attack and/or angina††, %, (number)	8.4 (218)	7.7 (212)	0.7*	3.4 (93)	2.5 (119)	0.9
Type 2 diabetes, % (number)	7.4 (196)	7.4 (204)	0.0	3.4 (90)	4.9 (186)	−1.5**
Plaque R-carotid: REF min, Tromsø-any, % (number)	46.8 (1238)	35.3 (997)	11.5**	38.3 (1039)	26.6 (1042)	11.7**

*P value <0.05; **p value <0.001.
†Values are mean (SD) or percentage (number). Age standardised according to the European Standard Population 2013.
‡The REFINE-Reykjavik study blood pressure (BP) measurement were adjusted for difference between measurements from arterial tonometry and sphygmomanometer measurements (see methods).
§Common carotid intima-media thickness.
¶Hypertensive medication.
††According to health questionnaire.
BMI, body mass index; LDL, low-density lipoprotein; REFINE-Reykjavik, Risk Evaluation For Infarct Estimates Reykjavik study.

site carotid plaque was higher in the REFINE-Reykjavik study than any or more right site plaque, in the Tromsø 6 study in both men and women. The changes in in cardiovascular risk factors by age was similar in both sexes and across age groups as is shown in online supplement 4 figure 1.

The mean far wall CIMT increased with age as can be seen in figure 1. The CIMT was higher in the age group 40–49 years in the Tromsø 6 study but was similar in the two studies after the age of 50 years in both men and women (figure 1).

As shown in figure 2, the prevalence curve for any right carotid plaques in the Tromsø 6 study lies between the prevalence curve for minimal or more carotid plaque and the prevalence curve for moderate or more carotid plaque in the REFINE-Reykjavik study (figure 2).

DISCUSSION

In this paper, we present the average prevalence of atherosclerotic plaque in the carotid arteries and average of cardiovascular risk factors in adult population of Reykjavik area in Iceland in the REFINE-Reykjavik study. We put the results in context with the results from the Tromsø 6 study. The main findings are that the evidence of manifest atherosclerosis, that is, the prevalence of carotid plaques, is similar in the two studies. Systolic blood pressure and LDL cholesterol levels were higher in the Tromsø 6 study, but the mean BMI was higher in the REFINE-Reykjavik study. The main limitation of the study is the methodological difference in the definition of atherosclerotic plaque in the carotids arteries as further discussed below.

The two population studies, the REFINE-Reykjavik study and the Tromsø 6 study, were conducted within the similar time interval (REFINE-Reykjavik study: 2006–2011, Tromsø 6: 2007–2008), which included both genders and both included middle-aged participants, mostly of Scandinavian origin and are therefore highly comparable. The prevalence curve for any carotid plaque by age and sex in the Tromsø 6 study lies in between the prevalence of minimal plaque and moderate plaque in the

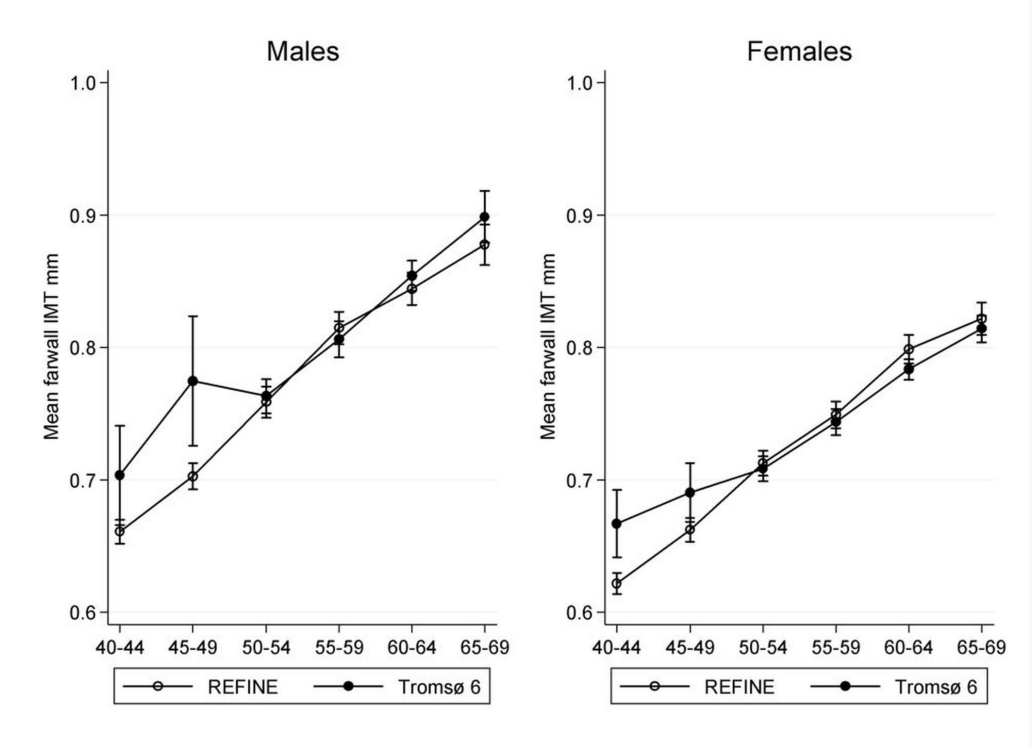

Figure 1 Mean far wall carotid intima-media thickness in the REFINE-Reykjavik study and Tromsø 6 study by age and sex. REFINE-Reykjavik, Risk Evaluation For Infarct Estimates Reykjavik.

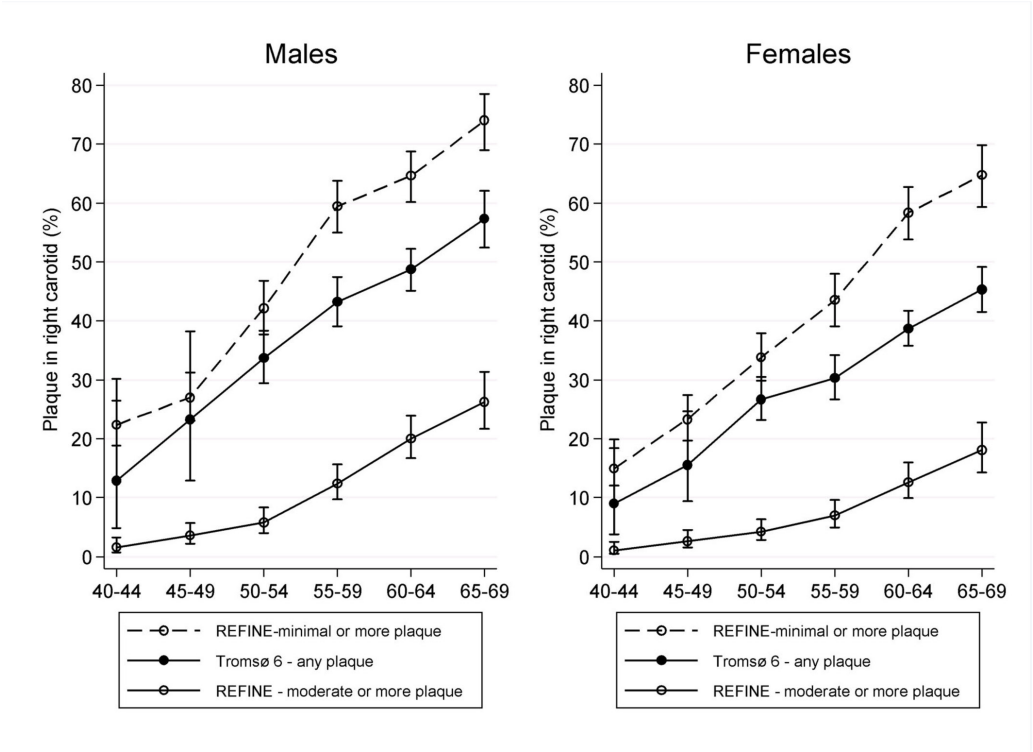

Figure 2 Prevalence of right carotid plaque in the REFINE-Reykjavik study and in the Tromsø 6 study by age and sex. REFINE-Reykjavik, Risk Evaluation For Infarct Estimates Reykjavik.

REFINE-Reykjavik study for both men and women. This can be seen in all age groups, and the increase with age is similar. The difference in prevalence of carotid plaque in the two studies is most likely due to a different definition of carotid plaque. In the REFINE-Reykjavik study, minimal plaque was defined as a small isolated thickening unifocal or multifocal, often with calcification approximately two times the adjacent normal CIMT. A moderate plaque was

defined as a clear, reasonably easily visualised plaque with or without calcifications that may be located on both near and far wall in the segment causing some diameter reduction. The definition of plaque presence in the Tromsø 6 study was of a '… localized protrusion of the vessel wall into the lumen'.[16] Focal calcifications without focal thickening or protrusion into the lumen were not regarded as atherosclerotic plaque in the Tromsø 6 study.[16] Since both studies show similar increase in plaque prevalence with increasing age and the threshold for definition of carotid plaque in the Tromsø 6 study seems to lie in between the definition for minimal and moderate plaque in the REFINE-Reykjavik study, we assume that the differences in plaque prevalence are mainly due to different definitions of plaque, although difference in prevalence of plaque cannot be excluded.

Comparison of the mean far wall CIMT between the REFINE-Reykjavik study and the Tromsø 6 study revealed close similarity between the two studies after the age of 50 years. The mean CIMT was higher in the Tromsø 6 study in participants under the age of 50 years than in the REFINE-Reykjavik study. However, the number of participants in this age group in the Tromsø 6 was relatively smaller compared with older age groups, and the CIs for the CIMT measurements were wider. We therefore concluded that the mean far wall CIMT was similar in the REFINE-Reykjavik study and the Tromsø 6.

It is clear that the need for a standardised definition of plaque and CIMT is important both for clinical practice, in order to increase the availability of ultrasound laboratories that can perform high-quality carotid plaque and CIMT evaluation and to increase comparability between future studies. Both in Europe and the USA attempts have been made in that regard. In 2008, the American Society of Echocardiography Carotid Intima-Media Thickness Task Force published a consensus statement.[17] There, carotid plaque was defined as 'the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or as a focal region with CIMT greater than 1.5 mm that protrudes into the lumen that is distinct from the adjacent boundary' .[17] In 2012, the Mannheim carotid IMT and plaque consensus (2004–2006–2011) was published where carotid plaque was 'defined as a focal structure that encroaches into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface'.[18] These two consensus statements give very similar definitions of plaque and will hopefully reduce confusion that different definitions can cause.

In all age groups, except for women aged 25–29 years, the mean BMI value was over 25 kg/m^2, the upper limit of normal weight according to WHO definition[19] .In the REFINE-Reykjavik study the mean BMI value for women was 26.7 kg/m^2 and for men 28.7 kg/m^2. More than a third of men over the age of 50 years were obese according to the WHO definition. In the Organisation for Economic Co-operation and Development (OECD) report 'Obesity update 2017', it is stated that, on average, one in five adults over 15 years of age is obese in the OECD countries. Iceland is near the OECD average in the same report.[20] We have previously analysed the trend in BMI in Iceland. According to the Icelandic Heart Association study, the mean BMI increased by 2 units in both genders (45–64 years old) from 1967 to 2007.[21] However, in the OECD report, it is revealed that obesity has stabilised in England, Italy, Korea and Spain.[20] Comparison with the Tromsø 6 study shows that the mean BMI was 0.9 units kg/m^2 higher in women and 0.8 kg/m^2 higher in men in the REFINE-Reykjavik study than in the Tromsø 6 study.

Almost a third of men aged 25–29 years smoked in the REFINE-Reykjavik study. This was somewhat lower than the average prevalence of smoking in developed countries according to a large international survey,[22] where about 38% of men in this age group smoked in 2012. Smoking decreased with age and was down to 17% in the 65–69 year old group in the REFINE-Reykjavik study. Comparison between the REFINE-Reykjavik study and the Tromsø 6 study showed that smoking was somewhat more prevalent in both men and women in the Tromsø 6 study. In men, the difference was 4% (21% REFINE-Reykjavik vs 25% Tromsø 6) and 9% in women (20% REFINE-Reykjavik vs 29% in Tromsø 6). Prevalence of women smokers in the REFINE-Reykjavik was similar to the prevalence of smoking among men in the same age groups (21%). This was similar as was seen in the Tromsö 6 study where smoking was even more prevalent among women (29.2%) than among men (25.4%). This is different from what was seen in many other developed countries where smoking among women is approximately half of the prevalence of smoking in men.[22]

Blood pressure should be below 140/90 mm Hg according to the European Society of Cardiology (ESC) 2012 guidelines. The mean values for blood pressure in the REFINE-Reykjavik study were well below the ESC targets for all age and gender groups. The mean blood pressure levels for men were 126/70 mm Hg and 116/69 mm Hg for women. We have previously shown that blood pressure levels have been dropping in Iceland from 1967 to 2007 in middle-aged men and women by approximately 20 mm Hg,[23] and this drop has been seen in all age groups, indicating a population effect rather than an effect of treatment with blood pressure-lowering drugs. However, the use of blood pressure-lowering drugs was very common in the REFINE-Reykjavik study in the oldest age groups. More than half of men and women in the age group of 65–69 years were taking blood pressure-lowering drugs. This high prevalence of drug use could lower the population mean in the oldest age groups. The blood pressure results in the REFINE-Reykjavik were 8 mm Hg lower in men (aged 40–69 years) and 10 mm Hg lower in women than in the Tromsø 6 study. The difference was similar in each age group. Difference in the use of blood pressure-lowering drugs could add to this highly clinically significant difference. This difference is similar in magnitude as the decline in blood

pressure in women from 1978 to 2008 in the Tromsø 6 study.[24]

According to the 2016 ESC guidelines for the management of dyslipidaemia, drug treatment should be considered if the 10-year risk of fatal cardiovascular disease exceeds 1% and LDL cholesterol is between 2.6 mmol/L and <4.0 mmol/L despite of lifestyle intervention.[25] Mean LDL cholesterol level in all age groups except in young women (25–29 years) was above this lower limit. The mean LDL cholesterol level was highest in 55–59 years men (3.4 mmol/L) and women 60–64 years (3.5 mmol/L). Comparison with the Tromsø 6 study revealed that in 40–69 years old, the mean LDL cholesterol was 0.5 mmol/L lower in men (3.3 vs 3.8) and 0.3 mmol/L lower in women (3.3 vs 3.6) in the REFINE-Reykjavik study than in the Tromsø 6 study. This difference was 15% in men and 11% in women. For comparison, the mean percentage lowering of LDL cholesterol after administrating 20 mg of simvastatin has been shown to be on average 35%.[26] In the REFINE-Reykjavik study, the LDL cholesterol was measured in participants after fasting from the evening before, whereas in the Tromsø 6 study, the LDL cholesterol was measured in non-fasting participants. In the Copenhagen General Population Study, the levels of LDL cholesterol was 0.2 mmol/L lower after meal than after fasting so the difference in LDL level between the REFINE-Reykjavik study and Tromsø 6 study could be even larger.[27]

We have previously published that TC levels in Iceland have been dropping as in other developed countries for the last decades.[28] The drop has been similar in both genders and all age groups. The mean drop in TC in the Icelandic population from 1967 to 2008 was 1.5 mmol/L in males and 1.6 mmol/L in females.[28]

The prevalence of diabetes has been historically been low in Iceland, but the prevalence of diabetes in men in the REFINE-Reykjavik study was almost identical to the prevalence of diabetes in men according to a population-based healthcare database in Sweden.[29] Another recent Swedish study shows that prevalence of diabetes was 59.8 per 1000 (6%) for men and 38.4 per 1000 (4%) for women 40–64 years old in 2010.[30] Comparison on the prevalence of type 2 diabetes in men between the REFINE-Reykjavik study and Tromsø 6 study also showed very similar results (7.4%). The prevalence was low in both studies among women (3.4% in REFINE-Reykjavik vs 4.9 in the Tromsø 6 study). The prevalence of diabetes in Iceland, Norway or Sweden has been, from a global viewpoint, relatively low. The prevalence of diabetes in USA in people older than 20 years was for example, according to the NHANES study, 13.4% in men and 10.2% in women in 2007–2010.[31]

In conclusion, the mean CIMT was similar in the REFINE-Reykjavik study and the Tromsø 6 study. The higher prevalence of carotid plaque in the REFINE-Reykjavik study was probably due to differences in the definition of plaque between the two studies. However, the mean for systolic blood pressure and mean LDL cholesterol levels were higher and smoking more prevalent in the Tromsø 6 study, but BMI was higher the REFINE-Reykjavik study.

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