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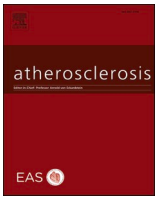

Sex differences in coronary atherosclerosis during the pre- and postmenopausal period: The Tampere Sudden Death Study

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ABSTRACT

Background and aims: Women are believed to be protected from coronary heart disease (CHD) by the effects of estrogen but detailed studies on the vessel wall level are missing. We aimed to measure sex differences in atherosclerosis during the premenopausal and postmenopausal periods directly at the coronary arteries.
Methods: We analyzed statistics for sex differences in CHD mortality in Finland in 2020. Coronary atherosclerosis was measured using computer-assisted morphometry in 10-year age groups of 185 white Caucasian women and 515 men from the Tampere Sudden Death Study.
Results: CHD mortality was rare in both women and men before 50 years of age. After 50 years of age, male mortality increased rapidly, with women reaching equal levels in the oldest age groups. In the autopsy series, there were no differences in fatty streak, fibrotic or calcified plaque areas, nor in the plaque area or stenosis percentage in coronary arteries between premenopausal women and men in the same age group. The plaque area remained 25 % smaller in both coronaries in postmenopausal women aged 51–70 years compared to men. In the oldest postmenopausal group (≥70 years), plaque area reached the level of men. In the postmenopausal period, coronary stenosis in the left anterior descending (LAD) artery remained lower among women.
Conclusion: We did not detect any major sex-difference in coronary atherosclerosis in the premenopausal period when women are considered to be protected from CHD. However, in line with CHD mortality statistics, postmenopausal women showed a slower speed of coronary atherosclerosis development compared to men.

1. Introduction

It is known that women lag behind men in coronary heart disease (CHD) morbidity and mortality by 10–15 years [1–3] but they catch up with men in the late menopause [4]. This difference is believed to be due to the protective effect of estrogen on coronary arteries, slowing the development of atherosclerosis in premenopausal women, and also by lower prevalence of CHD risk factors among women [1,2,5–7]. Because invasive studies of coronary arteries of healthy premenopausal women have not been performed, evidence supporting the estrogen protection theory during the reproductive years is experimental and indirect [8]. In animal experiments, it has been shown that estrogen prevented diet-induced early atherosclerosis in animals on a high-fat diet, suggesting a lipid-mediated mechanism [9,10]. Other indirect evidence comes from studies indicating a slight, but statistically non-significant, increase in CHD risk in women with early menopause, especially after bilateral oophorectomy [6]. Additionally, premenopausal women with hypoestrogenemia of hypothalamic origin have a higher occurrence of angiographically confirmed coronary artery disease (>70 % stenosis) compared to women with normal sex hormone levels [11].

If women were protected by estrogen and/or had lower levels of CHD risk factors during their reproductive years, a noticeable difference in atherosclerosis compared to men of the same age should be observed. A unique study [12] examined 262 heart transplant recipients aged 20–45 years using intravascular ultrasound (IVUS) and coronary angiography to measure atherosclerosis in their coronary arteries. The study found no significant difference in the prevalence of atherosclerosis (52 % in men and 51.7 % in women) based on intimal thickness of coronary arteries.

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Similarly, the few autopsy studies on young adults measuring coronary atherosclerosis areas did not find compelling differences between sexes during the premenopausal period. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study [13,14] found that fatty streaks and raised lesions covered only a small percentage of the coronary surface and differed by no more than 1 % or less between the sexes. The International Atherosclerosis Project (IAP) from the 1960s [15] reported that the intimal surface areas with raised lesions in the left coronary artery differed by 1–3.6 % among men and women aged 25–44. Sex differences were not observed in the thoracic and abdominal aorta, nor in the right coronary artery and left circumflex artery.

In the postmenopausal period, however, studies using cardiac computed tomography (CT) and magnetic resonance imaging (MRI) have shown that older female CHD patients often exhibit less calcified plaques [16,17] and less severe coronary stenosis [16,18] compared to men. In line, the IAP autopsy study [15] also reported slower progression of atherosclerotic lesions in women after menopause [19]. Other previous autopsy studies [1,7,20,21] assessed the severity of coronary atherosclerosis only visually or did not include men for comparison. To our knowledge, no studies have compared sex differences in the development of atherosclerosis during both pre- and postmenopausal periods using precise measurements.

In our study, we first analyzed national mortality statistics for sex differences in CHD mortality in Finland in 2020. We then investigated sex differences in the age-dependent progression of different atherosclerotic lesions and coronary stenosis in the Tampere Sudden Death Study - a unique autopsy series comprising pre- and postmenopausal women and men of a similar age. We used computer-assisted morphometry to measure the extent of atherosclerotic lesions in coronary arteries and to calculate the stenosis percentage from microscopic sections of coronary arteries.

2. Patients and methods

2.1. CHD mortality in Finland

We collected information from Statistics Finland on the age-dependent mortality rates due to CHD (ICD codes I20–I25) among women and men in Finland in 2020. In 2020, the overall mortality from all causes in Finland amounted to 55,488 (1 %) subjects out of a population of 5.531 million.

2.2. Tampere Sudden Death Study

The Tampere Sudden Death Study (TSDS) series comprises 515 white Caucasian men and 185 white Caucasian women aged 16–95 years subjected to a medicolegal autopsy at the Department of Forensic Medicine, University of Tampere, Finland, between 2010 and 2015 (Fig. 1). According to Finnish legislation, the indications for a medicolegal autopsy include sudden unexpected out-of-hospital death, accident, suspected suicide, or homicide. The Ethics Committee of Pirkanmaa Hospital District and the National Supervisory Authority for Welfare and Health approved the Tampere Sudden Death Study (TSDS) protocol (Permission number R09097).

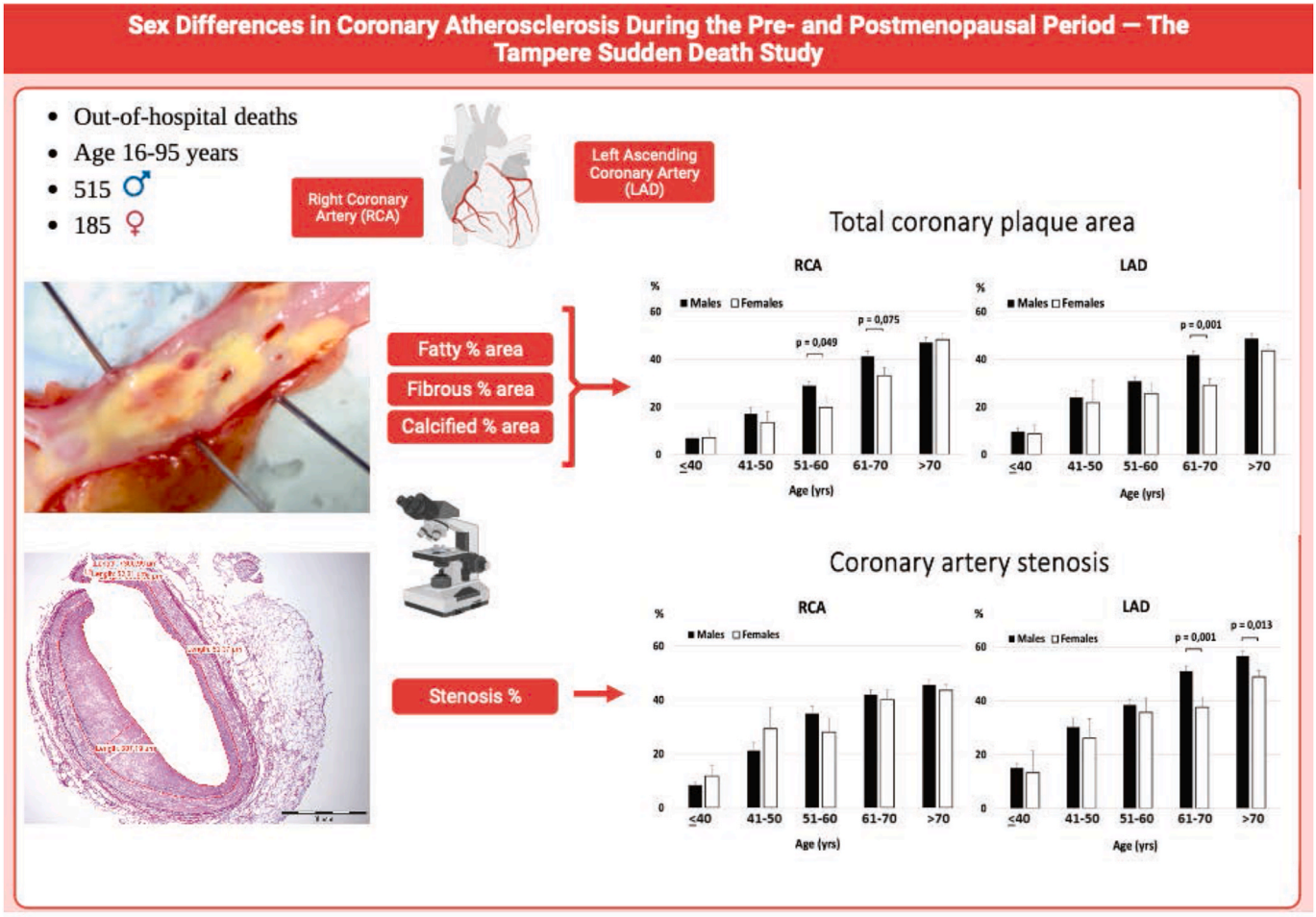

Fig. 1. Study protocol of the Tampere Sudden Death Study.
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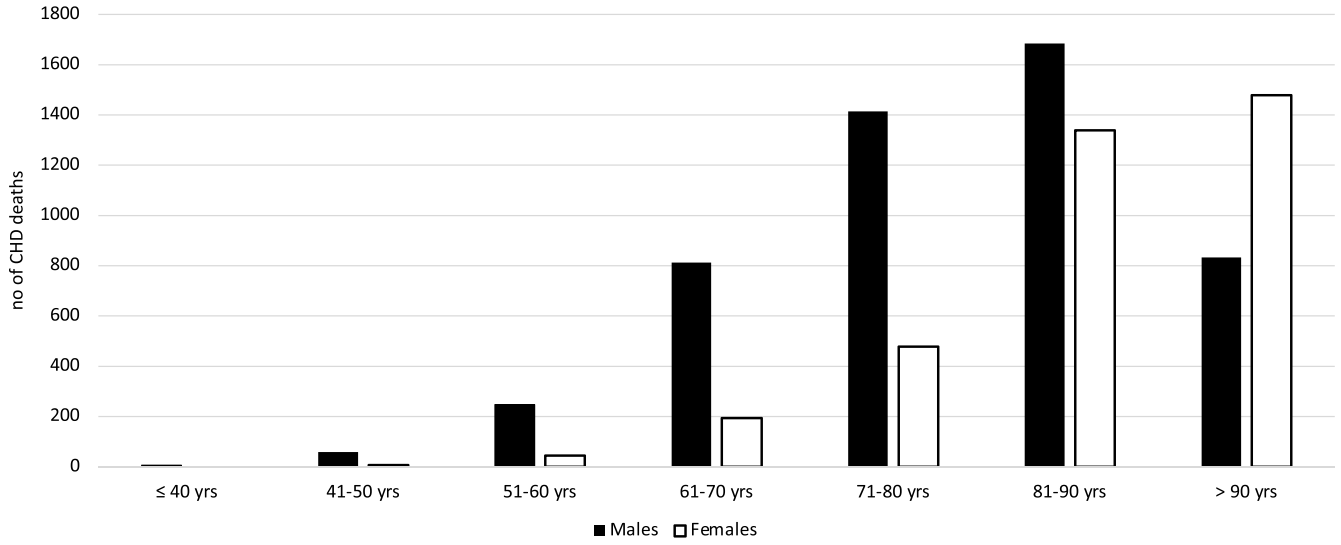

Fig. 2. The age-dependent number of deaths from CHD in men and women in Finland in 2020.

At autopsy, the coronary arteries were removed and transferred fresh to the laboratory for measurement of atherosclerotic lesion surface areas using computer-assisted morphometric software (Olympus Cell-D). The first 5 cm piece was measured from the right (RCA) and left coronary artery (includes the left main and proximal part of left anterior descending (LAD) coronary artery). Following surface measurements, cross-sections were taken from the most stenotic segment of the left and right coronary arteries and the healthiest distal segment of the same artery to be fixed in 10 % buffered formalin and embedded in paraffin. Histological sections were stained with van Gieson or MOVAT Pentachrome, and the stenosis percentage was measured using morphometry.

In females, menopause usually occurs between the age 45–55 years. In 17 cross-sectional and observational studies across 7 countries, it was

Table 1
Age, BMI, and causes of death by sex in the TSDS study.

	Women (n = 185)	Men (n = 515)	Age-adjusted *p*-value
Age[a]	68.4 ± 17.1	61.7 ± 15.7	N/A
≤ 40	14 (7.5)	54 (10.5)	
41-50	11 (5.9)	50 (9.7)	
51-60	26 (14.1)	107 (20.8)	
61-70	39 (21.1)	153 (30.7)	
> 70	95 (51.4	151 (29.3)	
BMI[b]	29.1 ± 72	28.3 ± 6.3	0.101
Cause of death[c]			
Diseases	143 (77.3)	398 (77.3)	0.097
All CAD	62 (33.5)	192 (37.1)	0.002
CAD without MI	21 (11.4)	74 (14.2)	0.006
All MI	41 (22.2)	118 (22.9)	0.186
Acute MI	39 (21.1)	99 (19.2)	0.619
Cardiomyopathy	7 (3.8)	50 (9.7)	N/A
Mitral or aortic valve	6 (3.2)	9 (1.7)	N/A
Other diseases	79 (42.7)	231 (44.7)	N/A
Accidents	25 (13.3)	73 (14.2)	0.534
Suicide	11 (5.9)	38 (7.4)	0.895
Homicide	2 (1.1)	0 (0)	N/A
Undefined, non-violent	4 (2.2)	6 (1.2)	N/A
Left anterior coronary artery (LAD)[d]			
Stenosis	40.6 ± 24.7	44.3 ± 26.0	<0.0001
Fatty streak area	5.3 ± 9.9	5.8 ± 9.8	0.781
Fibrous plaque	10.4 ± 13.5	12.9 ± 15.2	0.010
Calcified plaque	18.2 ± 25.8	17.5 ± 24.2	0.041
Total plaque area	34.0 ± 25.2	36.4 ± 24.1	<0.001
Right coronary artery (RCA)[d]			
Stenosis	36.9 ± 24.8	36.0 ± 26.7	0.101
Fatty streak area	9.2 ± 13.5	7.2 ± 11.5	0.145
Fibrous plaque	11.4 ± 14.0	12.2 ± 14.0	0.034
Calcified plaque	15.6 ± 24.1	15.0 ± 24.0	0.099
Total plaque area	36.1 ± 8.1	34.4 ± 26.6	0.008

[a] years, mean ± SD, n (%).
[b] kg/m^2, mean ± SD.
[c] no of cases (%).
[d] percentage area ±SD.

found that the median age of menopause was 50 years [22]. We thus applied the median 50 years of age to classify the series into premenopausal and postmenopausal period.

Statistical analyses were performed with Version 27 of IBM SPSS statistics software (IBM SPSS Statistics for Windows, Version 24.0. IBM Corp. 2016. Armonk, NY). Chi-squared or Fisher's exact test was used for statistical comparisons of categorical variables. ANOVA and ANCOVA with age as covariate and sex as a fixed factor were applied to calculate differences in continuous variables between the groups. Logistic regression (enter mode) was used to perform analyses of the association between the occurrence of myocardial infarction (MI) age and sex. Violin plots were applied to show the distribution of the data.

3. Results

3.1. Sex differences in CHD mortality in Finland

Out of the total 55,488 deaths in Finland in 2020, 8600 (14.5 %) were attributed to CHD, with 5060 (58.8 %) being men and 3540 (41.2 %) women. CHD mortality remained low for both sexes until the age of 50, with only 71 (0.8 %) CHD deaths occurring before this age (Fig. 2). Among these deaths, 65 (91.5 %) were men and 6 (8.5 %) were women. Subsequently, mortality rates began to rise among men. In the postmenopausal period, women's mortality rates also started to increase, approaching the level of men and surpassing them in the oldest age group. Considering women's longer life expectancy, they constitute a larger proportion of the oldest age group. Consequently, the number of deaths per 100,000 within the male population slightly remains higher compared to women [23].

3.2. Characteristics of the Tampere Sudden Death Study series

On average, female decedents were older than males (68.4 *vs* 61.7 years; $p < 0.0001$) (Table 1). In age-adjusted analyses men had died more often from all coronary artery disease (CAD) ($p = 0.002$) and CAD without MI ($p = 0.006$), whereas there was no sex difference in deaths due to all MI (old scar and acute MI) or acute MI.

Women had a significantly ($p < 0.0001$) smaller percentage of coronary stenosis than men in the left anterior descending (LAD) coronary artery (40.6 % *vs* 44.3 %) but not in the right coronary artery (RCA). The fatty streak area was almost equal in women and men in LAD, whereas women tended to have larger fatty streak area in RCA. In women, the fibrous plaque area was smaller in LAD ($p = 0.010$) and in RCA ($p = 0.034$). In contrast, the calcified plaque area tended to be larger in

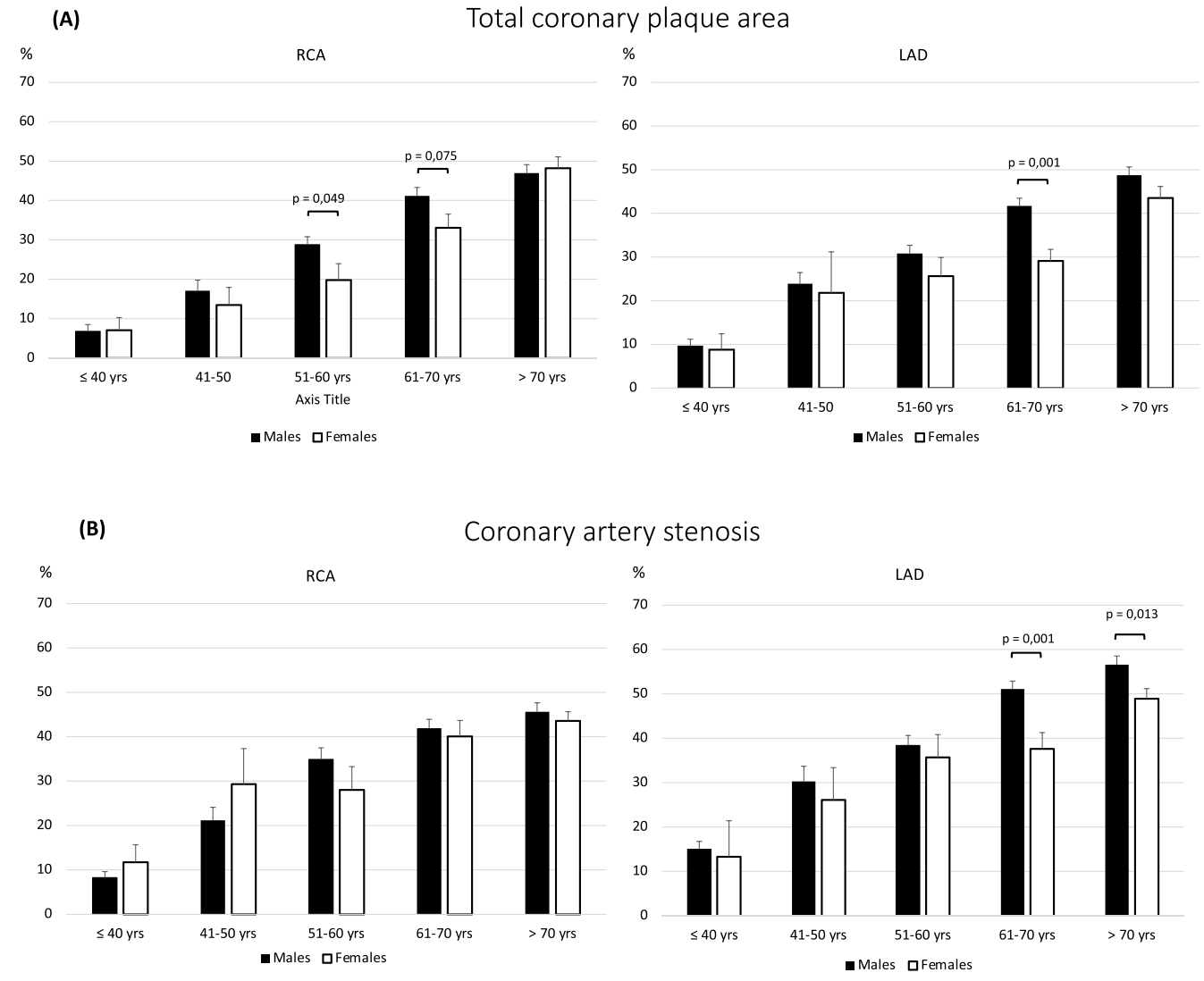

Fig. 3. Age-dependent differences in total coronary plaque area (A) and coronary artery stenosis (B) between men and women.
Values are presented as mean percentage + SE. RCA: right coronary artery, LAD: left anterior coronary artery (including the left main coronary artery).

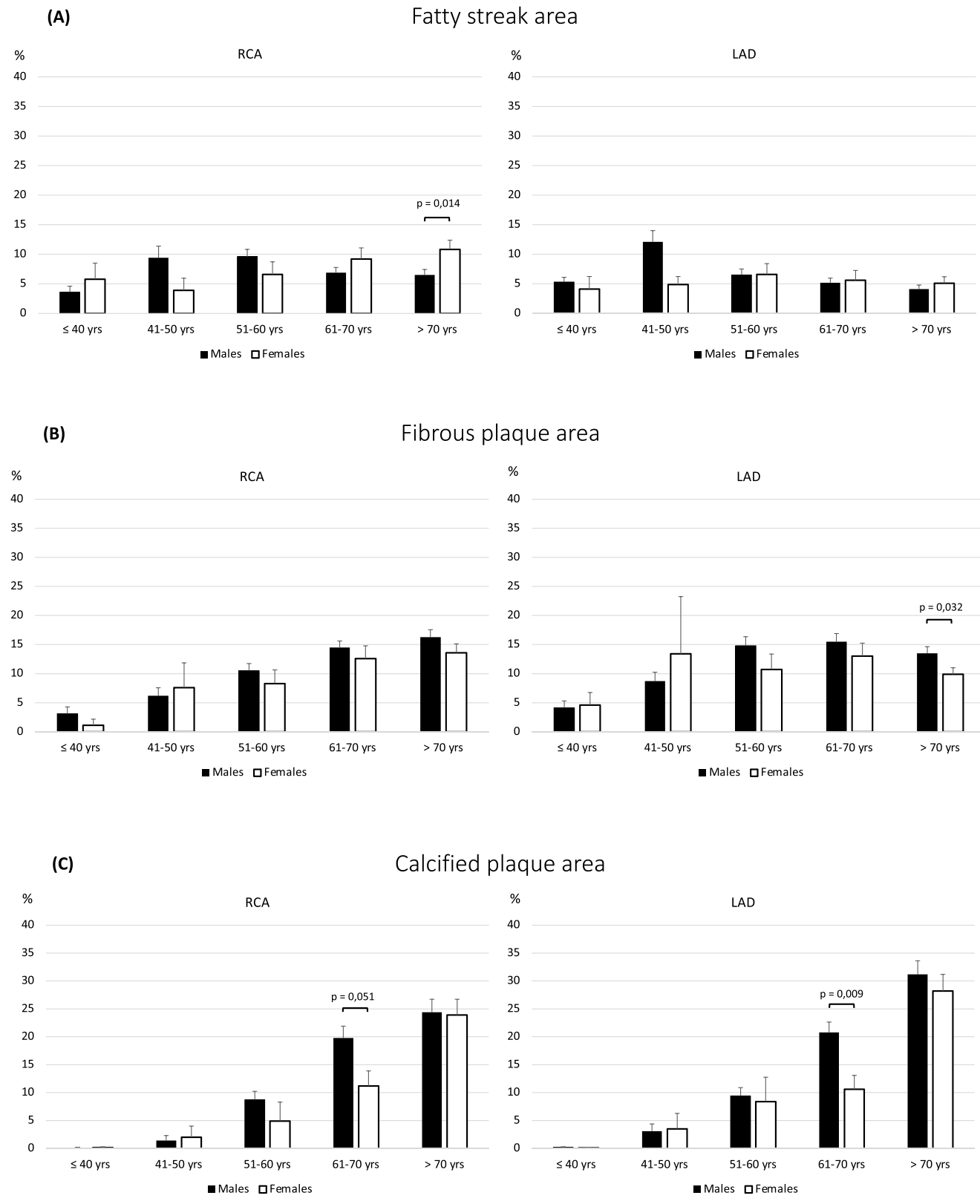

Fig. 4. Age-dependent differences in fatty streak area (A), fibrous plaque area (B), and calcified plaque area (C) between men and women. Values are presented as mean percentage + SE.
RCA: right coronary artery, LAD: left anterior coronary artery (including the left main coronary artery).

women in both coronaries. Women had a smaller total plaque area in LAD ($p < 0.0001$) but a larger area in RCA ($p = 0.008$).

3.3. Age-dependent differences in coronary atherosclerosis in women and men

In the age-adjusted analysis, there were no notable differences in the total plaque area between premenopausal women (<50 years) and men in the same age group for both RCA and LAD (Fig. 3A). However, early postmenopausal women aged 51–60 years had an average 24 % smaller total plaque area compared to men (RCA: $p = 0.049$; LAD: $p = 0.264$), and women aged 61–70 years had a 25 % smaller total plaque area (RCA: $p = 0.075$; LAD: $p = 0.001$). The total plaque area in the oldest women reached the same level as men. The percentage of coronary artery stenosis (Fig. 3B) exhibited no significant age-dependent sex difference in RCA. However, in LAD, women aged 61–70 years ($p = 0.001$) and the oldest age group ($p = 0.013$) had significantly lower stenosis percentages. Among individuals aged 50 years or younger, 33 % of women and 37.5 % of men had >50 % stenosis in either coronary artery.

There were no significant differences in fatty streak areas between men and women in any age group (Fig. 4A), except for the oldest age group where women had larger fatty streak area in RCA ($p = 0.014$).

The fibrous plaque area (Fig. 4B) did not differ significantly by sex in the premenopausal period but tended to be smaller in RCA and LAD among postmenopausal women than in men of the same age. This difference was statistically significant in LAD in the oldest age group ($p = 0.032$). The area of calcified plaques (Fig. 4C) in RCA and LAD was smaller in postmenopausal women than in men up to the age of 61–70 years (RCA $p = 0.051$; LAD $p = 0.009$), reaching the level of men in the oldest age group.

In violin plots of the data, it was observed that the distribution of the parameters between men and women was quite similar (Supplementary Fig. 1S).

If we restrict the cases only to those who have died of CHD, only individuals over 50 years of age remain to be analyzed since there were only 2 women and 7 men younger than 50 years who died of CHD. Among those over 50 years of age, the results do not change: over 50-year-old men who died of CHD have more severe coronary heart disease than females of the same age group, but in the oldest age group women reach the level of severity of CHD.

We then compiled cases of women younger than 40 years into one table to illustrate the presence of atherosclerotic changes (Supplementary Table 1S). Nine of the 14 women under the age of 40 died of unnatural causes, and five died from diseases. Microscopic photographs (Fig. 5) illustrate some typical cases of atherosclerotic lesions found among these women. It can be observed that atherosclerotic changes are not rare among premenopausal women, although they seldom appear before the age of 30.

3.4. Differences in atherosclerosis between premenopausal and postmenopausal women

The atherosclerotic lesions were generally mild in premenopausal women, with the total lesion area usually being less than 10 % in women younger than 40 years and increasing to 10 %–30 % in women aged 41–50 years (Fig. 3A and B). After menopause, total plaque area and stenosis percentage increased linearly up to the oldest age group, where the total plaque area was approximately 50 % of the surface of coronary arteries. The fatty streak area and fibrous plaque area (Fig. 4A and B) remained almost at the same level throughout the age groups. The increase in total plaque area is explained by the increase in the calcified plaque area (Fig. 4C), which increased to 30 % in LAD.

4. Discussion

In line with knowledge on women's lower CHD mortality [1–3], we found that mortality from CHD in Finland in 2020 was extremely low in both women and men up until 50 years of age, most of the deaths occurring in men. Mortality among Finnish men increased significantly after 50 years of age, while the increase in women was observed a decade later, reaching similar levels to men in the oldest age groups. This sex difference is believed to be mainly mediated by estrogen's beneficial effects on atherosclerosis development during reproductive years and beyond menopause [5]. Contrary to the belief that premenopausal women are protected from CHD, we found early atherosclerotic changes in premenopausal women before age 50, with no difference in total lesion areas compared to men of the same age. However, in the postmenopausal period starting at 50 years of age, men exhibited a faster increase in total, fibrous, and calcified plaque areas, as well as stenosis percentage, particularly in the LAD. This sex difference diminished in the oldest age group, along with CHD mortality in the national causes of death register. The differences in the atherosclerosis between the coronary arteries may be due to alterations in the hemodynamics between the RCA and LAD [24,25].

Our study challenges the theory of estrogen-related protection by revealing no sex difference in coronary atherosclerosis during the

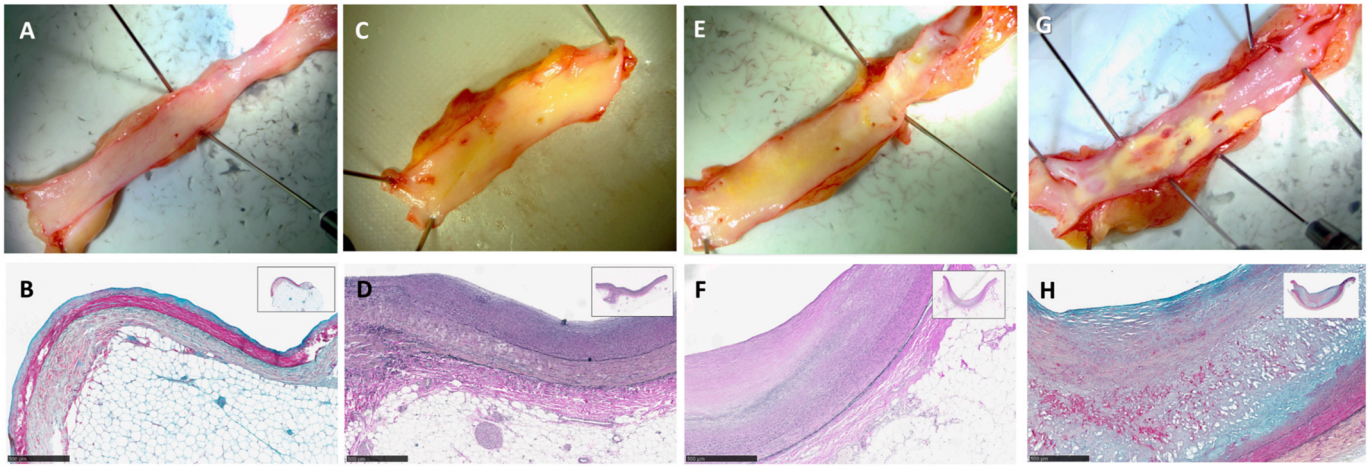

Fig. 5. (A–B) LAD of a 16-year-old female suicide victim (Case 1), showing slight intimal cell-rich hyperplasia (AHA type I, MOVAT Pentachrome). (C–D) Thick intimal hyperplasia with occasional foam cells (AHA type II, van Gieson) in RCA of a 25-year-old female victim of a traffic accident (Case 5). (E–F) Calcifying fibroatheroma in RCA (AHA type Va, Van Gieson) of a 30-year-old female (Case 9) who died of a diabetic coma. (G-H) Calcifying fibroatheroma with intraplaque spotty hemorrhages in LAD (AHA type VI, MOVAT Pentachrome) of a 39-year-old female (Case 14) who died of an intracerebral hemorrhage (ICH).

premenopausal period. This finding is supported by the PDAY study [13], where combined fatty streak and fibrous plaque areas in women (7.9 %) and men (9.0 %) aged 30–35 years were similar to the areas we measured in women (6.9 %) and men (6.8 %) under 40 years of age. Moreover, our results align with the International Atherosclerosis Project (IAP) autopsy findings from the 1960s, which showed no sex difference in the extent of fatty streaks or raised lesions in premenopausal women compared to men [26]. However, our study conflicts with a retrospective autopsy study conducted in New York in 2011 [7]. That study reported more than 50 % coronary stenosis in 84.9 % of women and 93.8 % of men in a group of decedents aged 21–54 years. In our prospective study, 33 % of women and 37.5 % of men aged 50 years or younger had more than 50 % coronary stenosis. The previous study did not measure atherosclerosis and assessed coronary stenosis solely through visual approximation. Additionally, the female population in that study had a more diverse racial composition compared to males [7].

During the transition to menopause around the age of 50, estradiol levels in women decrease rapidly to 20 % of the levels observed during reproductive years [27]. Consequently men, who continuously produce estrogen via testosterone metabolism, have similar estradiol levels than postmenopausal women [28]. Thus, the diminished estrogen levels after menopause may not confer any beneficial effects on atherosclerosis development. However, contrary to this expectation, our findings indicate that the total coronary plaque area and calcified lesion area remained significantly lower in postmenopausal women until the age of 70, when women caught up with men in these aspects. These results are supported by a large study using multidetector CT angiography in patients aged 48–74, which revealed that women had a lower number of segments containing calcified and mixed plaques compared to men [16].

Studies on the association between endogenous sex hormones and incident CVD events in women have yielded conflicting results. In the Multi-Ethnic Study of Atherosclerosis (MESA) [29] study and Copenhagen City Heart study [27], higher levels of testosterone were associated with increased cardiovascular disease (CVD) and CHD, whereas higher endogenous estradiol levels were associated with a lower CHD risk. However, in a nested case-control study among women in the Women's Health Study, estradiol levels were not associated with risk of CVD in hormone therapy users or nonusers [30]. Similarly, in Rancho Bernardo Study of Healthy Aging, endogenous estrogen or testosterone concentrations did not predict cardiovascular death or death from ischemic heart disease in postmenopausal women [31].

The place of hormone replacement therapy in the prevention of CHD mortality in postmenopausal women has caused a large debate because the Women Health Initiative (WHI) study failed to show any benefit [32]. However, recent registry-based and case-control studies have shown that estradiol-based hormone therapies are associated with lower CHD mortality risk the earlier the therapies are initiated [33,34].

An alternate hypothesis for the gender differences has been presented [35]. According to this theory, instead of estrogen, testosterone is the culprit, explaining older men's higher risk of heart disease. An association between low serum testosterone levels, andropause, and increased carotid artery intima-media thickness has been reported in middle-aged men [36].

Differences in CHD risk factors and lifestyle may contribute to the variation between sexes in atherosclerosis and myocardial infarction. A study based on the follow-up data of the North Karelia Project in Finland [2], involving 14,786 men and women aged 25–64, revealed that disparities in risk factors, particularly high-density lipoprotein (HDL) cholesterol and smoking, accounted for almost half of the variation in CHD risk between men and women. While premenopausal women had lower total cholesterol levels compared to men, this difference diminished with age. Smoking was consistently the most significant risk factor differing between sexes across all age groups. For instance, among postmenopausal women aged 50–64, only 10.1 % were smokers, while the corresponding figure for men was 35.1 %. Similarly, in a large meta-analysis from Asian Pacific region, 54 % of the men and 7 % of the women were smokers. Hence, smoking was the biggest risk factor differing between the sexes [37].

Besides differences in sex hormone levels, it has been suggested that a possible underlying mechanism affecting the severity of cardiovascular diseases may be due to a differential gene regulation in men and women, particularly in sex steroid–responsive genes [28]. In men also producing small amounts of estrogen [28], genetic polymorphisms in the ERα gene have been found to modify the severity of coronary atherosclerosis [38,39]. However, because the distribution of the genotypes did not differ between the sexes [40], genetic polymorphisms in estrogen receptors may explain individual variation in coronary atherosclerosis or the risk of myocardial infarction. Genetic polymorphisms in estrogen receptors may thus not explain sex differences in CHD.

4.1. Limitations and strengths

The limitations of our study include that we do not have information about the victims' hormone levels, menopausal status, or possible hormone replacement treatment. However, slower development of coronary atherosclerosis in postmenopausal women was observed already in the International Atherosclerosis project from the 1960's before the era of hormonal replacement therapy. While the medicolegal autopsy series is the best series to represent a cross-section of the general population, it is biased by the overrepresentation of victims of suicide and other violent deaths and there are more heavy alcohol users than in the general population. Due to Finnish legislation, this series is unique because it comprises all out-of-hospital sudden deaths, among which cardiac deaths are the most common. The Finnish population is also relatively homogeneous in terms of race, the standard of living, and health care. Although the COVID19 pandemic was going on in Finland in 2020 and caused an increase in mortality, it had no significant effect on the specific mortality from CHD (ICD codes I20–I25).

4.2. Conclusion

In the national death registry, mortality from CHD was low among both sexes before the age of 50 years. Thereafter, it increased rapidly among men, with women catching up after 80 years of age. In our autopsy series the atherosclerotic disease burden in premenopausal women considered to be protected from CHD did not differ from men of the same age, with both sexes showing only mild disease. In contrast, postmenopausal women who are no longer protected by estrogens, had a lower extent and severity of atherosclerosis at the age of 50–70 years, after which the atherosclerosis rapidly accelerated to the same level as men. In women, the total plaque area increased evenly throughout the age groups, mainly due to the increase in the calcified plaque area, since the fatty streak area and fibrous plaque area remained the same in all age groups. It thus seems that, besides estrogen, other explanations—such as higher prevalence of acquired CHD risk factors among aging men as well as possible andropause-related effects on increased CHD risk among men—might explain the sex differences in the speed of atherosclerosis development.

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CRediT authorship contribution statement

Emma Hakamaa: study conception and design, analysis and interpretation of results, draft manuscript preparation, All authors reviewed the results and approved the final version of the manuscript. **Sirkka Goebeler:** analysis and interpretation of results, All authors reviewed the results and approved the final version of the manuscript. **Mika Martiskainen:** analysis and interpretation of results, All authors reviewed the results and approved the final version of the manuscript. **Anne-Mari Louhelainen:** analysis and interpretation of results, All authors reviewed the results and approved the final version of the manuscript. **Katja Ahinko:** study conception and design, analysis and interpretation of results, draft manuscript preparation, All authors reviewed the results and approved the final version of the manuscript. **Terho Lehtimäki:** study conception and design, All authors reviewed the results and approved the final version of the manuscript. **Pekka Karhunen:** study conception and design, analysis and interpretation of results, draft manuscript preparation, All authors reviewed the results and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2024.117459.

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