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The Impact of Geographical and Regional Differences on the Female Disparity in Cardiac Diseases

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ABSTRACT

Objective: *Since the beginning of the century, the number of cardiac interventions has increased massively and has improved outcomes after cardiac events. The efforts have proven effective with a falling incidence of new cardiovascular diseases. In a small uniform country with a free, fully tax-supported medical system, the previously demonstrated regional differences are not readily explained, and local within-country differences have received little attention. The study aimed to evaluate geographic divergence in referral and invasive treatment of cardiovascular diseases, with a focus on municipality and sex.*

Materials and Methods: *The mandatory Western Denmark Heart Registry was used to identify all first-entry adult cardiac procedures performed in three western regions from 2014–2020. To compensate for municipality differences in inhabitant composition, only patients aged 40 years or older were included, resulting in a cohort of 110,199 first-entry patients.*

Results: *Significant differences were found between sexes in referral (females 42.3%) and invasive cardiac treatment (females 19.8% vs. males 38.8%), as well as between municipalities. Females had higher mortality than males after invasive treatments (5-year mortality: females 20.2% vs. males 16.8%), while the opposite result was found after diagnostic evaluation only (5-year mortality: females 7.8% vs. males 11.2%). Marked differences were seen between municipalities without a visible explanatory pattern.*

Conclusion: *The augmented screening by CTA has likely resulted in improved and faster access to treatment of cardiovascular diseases, but females are still referred less often than males for investigation and higher mortality following invasive treatments remains. Major differences in referral and mortality between regions and municipalities are not readily explained.*

Keywords

Cardiovascular disease, Female discrepancy, Regional differences, Incidence ischaemic heart disease, Risk.

Introduction

During the last decades, the health system has worked intensively with a sizable increase in diagnostic cardiac procedures and slightly more invasive treatments [1,2] in order to attenuate the frequency and improve the outcomes of cardiovascular diseases (CVD). Improved surgical procedures, the introduction of percutaneous coronary interventions (PCI), and an increased focus on prevention have changed the treatment opportunities. Consequently, between 2000–2019, the CVD mortality in Denmark has declined from 253 to 110 per 100,000 age-standardised persons [3].

Subsequently, the incidence and mortality of cardiovascular, and especially ischaemic heart disease (IHD) have declined substantially in many countries [4,5], but despite the great reductions, particularly in the developed countries, CVD still accounts for over 30% of worldwide deaths, with IHD being the leading cause [4,6,7].

It is well known that rates and trends differ between countries, and the fall in some, especially western countries, indicates a large potential for future additional gains on the global level. However, a less focused area is in-country regional differences, as pointed out in previous studies [8,9].

Despite being referred for cardiac diagnostic evaluation close to their CVD prevalence and the overall improvement in treatment possibilities and outcomes, females still receive fewer invasive treatments than males and present substantially higher mortality after invasive treatments [10-13]. Further, the overall approach to resource allocation for prevention and treatment efforts has traditionally used a helicopter perspective, with the risk of overlooking local regional in-country differences.

The aim of this study was to evaluate local and geographic divergence in diagnostic procedures and invasive cardiac treatments of CVD with a focus on regions, municipalities, and sex.

Material and Methods

Since 1999, the mandatory Western Denmark Heart Registry (WDHR) has collected information on all cardiac procedures in three Danish regions, covering approximately 60% of the Danish uptake area, with a population of more than 3.2 million inhabitants. WDHR encompasses risk factors, diagnosis, results, and outcome of cardiac diagnostic and interventional procedures performed in adult patients. The WDHR commenced with invasive coronary angiography (ICA), percutaneous coronary interventions (PCI), and cardiac surgery in 2000. Computed tomography angiography (CTA) and transcatheter aortic valve replacement (TAVR) were added in 2007/2008. Data are registered prospectively, including detailed patient risk-, procedure-, and care-related data and fully integrated into daily clinical practice [14].

All Danish citizens have a unique civil personal registration (CPR) number assigned at birth or immigration and kept throughout life, enabling cross-linking between different health and civil registries, ensuring feasibility of conducting large, population-based studies with relevant outcome follow-up on all the procedures and treatments [15]. The civil patient information in WDHR is updated against the CPR register every night. When a patient dies, the home address information is deleted in WDHR. Subsequently, a field with municipality information, at time of the procedure, was added to WDHR late in 2013 to facilitate control and analysis of municipality and region impact.

The municipalities in the Western part are relatively small and uniform with 621 (507–722) km² and a population of 69 (62–90) inhabitants per km² [16]. However, regions and municipalities might be very different in inhabitant composition due to differences in age and educational/working possibilities. To address this, the analysis was based on inhabitants aged 40 or older, thus minimizing differences in the age composition particularly in larger cities with high rates of students and new families. Inhabitants in individual municipalities and regions are shown in Supplement 1.

Study Population

From the full WDHR dataset, all first-entry relevant procedures were obtained by excluding patients without valid ID, referrals for non-cardiac indication, patients with a history of invasive cardiac treatment and all subsequent procedures after the index procedure in patients undergoing multiple procedures (Figure 1). To have a full dataset of comparable procedures with municipality information, records from 2014-2020 were isolated and considered for eligibility. Patients living in municipalities outside the WDHR standard uptake area, Greenland, and foreigners were excluded from detailed analysis.

Data handling was approved and registered by the Danish Data Protection Agency (1-16-02-455-21). Written consent is not required for registry-based studies according to Danish legislation. The handling and use of data fully complied with the agency's directions.

Outcome parameters

The main analysis was municipality differences and associations between diagnostic procedures and any following invasive treatment procedures, i.e., PCI, cardiac surgery, and TAVR with primary focus on sex and municipality differences.

The primary outcome was the number of procedures and mortality in relation to municipality population aged more than 40 years.

Statistical Analyses

Patients were divided by municipality, age, sex, and procedure type for detailed statistical analyses. Categorical variables were analysed using the χ^2-test, and continuous variables using Student's independent t-test and ANOVA. Kaplan–Meier survival curves were used to evaluate outcomes over time. Analyses were performed with MedCalc® software version 23.4 (Ostend, Belgium). A probability value of <0.05 was used to define statistical significance.

Results

The foundation for the study was the 274,617 registered first-entry cardiac procedures in WDHR at the end of 2020. To secure that all procedures had registered municipality information at the time of the procedure, the number was narrowed down to 117,357 during 2014–2020. Further exclusions were 2,339 patients living outside the WDHR normal uptake area and finally 4,819 patients younger than 40 years, ending with a cohort of 110,199 first-entry patients (Figure 1).

The number of first-entry procedures per year per 10,000 inhabitants allotted by municipality and sex is shown in Figure 2. Overall, the number of procedures was 42.3% higher in males than females (114 vs. 80 per 10,000), and the differences between municipalities were even greater, ranging from 90 to 134 in males and from 59 to 98 in females, a difference of 48.2% and 67.4%, respectively. The picture is even more diverse when viewing the patients achieving an invasive cardiac treatment or cardiac surgery within six months after the diagnostic procedure. The difference

between sexes was 185% (average males 449 vs. females 157 per 100,000 inhabitants), and an additional sex variance of 56% in males and 160% in females (Figure 2).

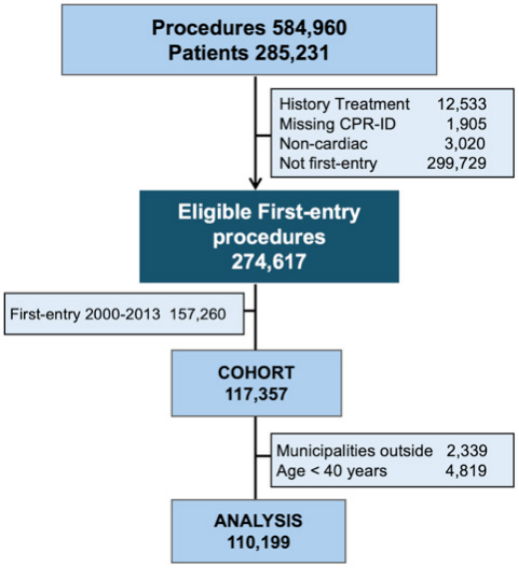

Figure 1: Screened procedures from WDHR 2000-2020 and the exclusions. After primary exclusion is established first entry procedures, which was narrowed to 2014-2020 to secure all have a valid municipality. CPR=civil personal registration; non-cardiac a mixture of research, projects, screening without symptoms and before non-cardiac surgery.

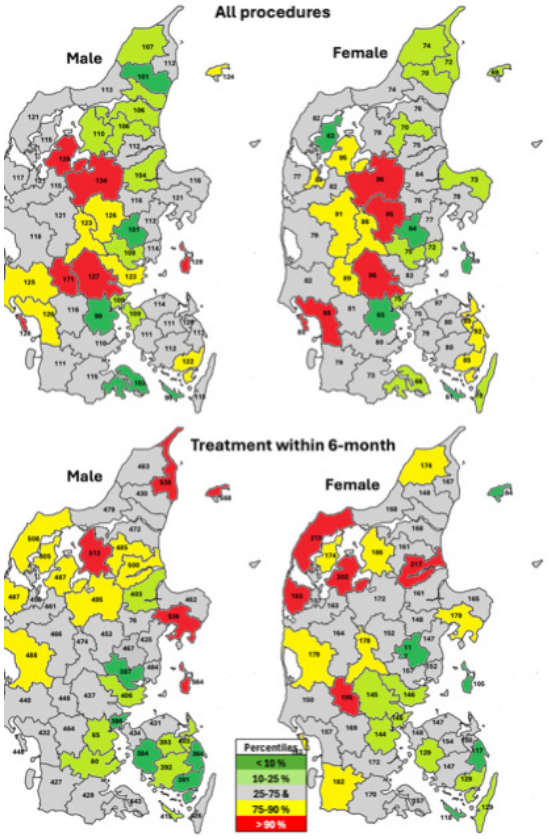

Figure 2: Number of first-entry procedures per year per 10.000 inhabitants (upper panels) and the numbers of cardiac invasive treatment procedures within 6 month after diagnostication per 100,000 inhabitants (lower panels) divided on municipality and sex.

Overall, the number of procedures per year per 100,000 inhabitants was higher in males compared to females (1153 vs. 804; $p < 0.0001$, t-test). Concerning diagnostic evaluation without later invasive treatment, the average number of procedures was slightly higher in males than females, being 681 vs. 623 ($p = 0.0014$, t-test), while the difference was substantially higher in patients submitted to invasive treatment within six months after the index diagnostic procedure with 453 vs. 159 ($p < 0.0001$, t-test) (Figure 3).

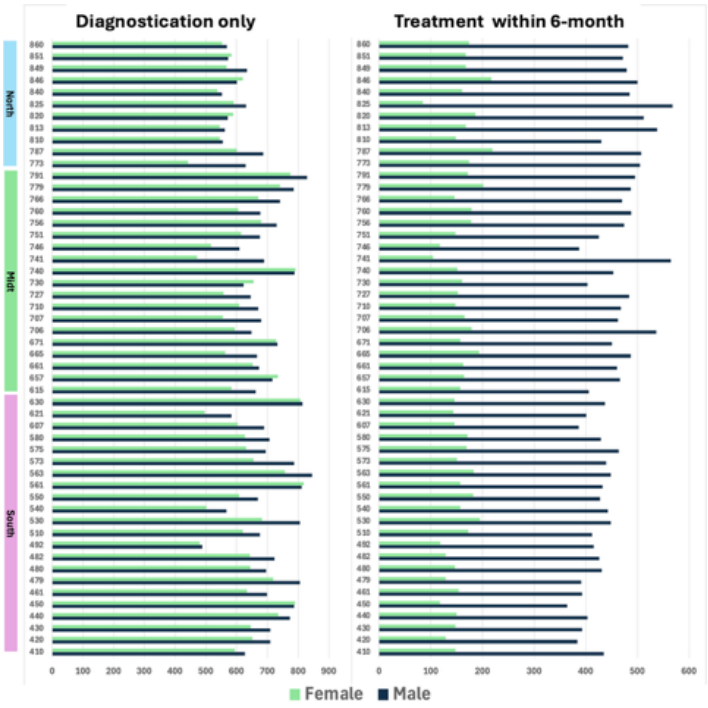

Figure 3: Average number of procedures per year pr 1000 inhabitants divided on diagnostication only (left panel) and invasive treatment within 6 month (right panel) divided on municipality and sex. Significant difference in numbers in both municipality and sex ($p<0.001$, 2-way ANOVA).

Females were on average 1.0 year older than males (Figure 4), but with great diversity between municipalities ranging from minus 0.6 to plus 4.5 years ($p < 0.001$). The figure also demonstrates that patients from Region North were older than the two other regions, being 63.7 vs. 62.5 and 62.3 in males and 64.8 vs. 63.0 and 62.6 in females.

The figure further shows that ICA was the most preferred diagnostic tool in Region North (57.5% ICA), while CTA was the dominant diagnostic tool in Region Midt (55.2%) and Region South (53.4%). Region North has one full cardiac centre and one hospital performing CTA, while both Region Midt and Region South each have a full cardiac centre, two hospitals with ICA and CTA, and additional three hospitals performing CTA in Region Midt and one hospital in Region South, which together reflects the higher use of CTA in Region Midt. The number of CTA procedures was significantly higher in municipalities with a hospital performing CTA at 55.1% vs. 49.7% ($p < 0.001$; ANOVA).

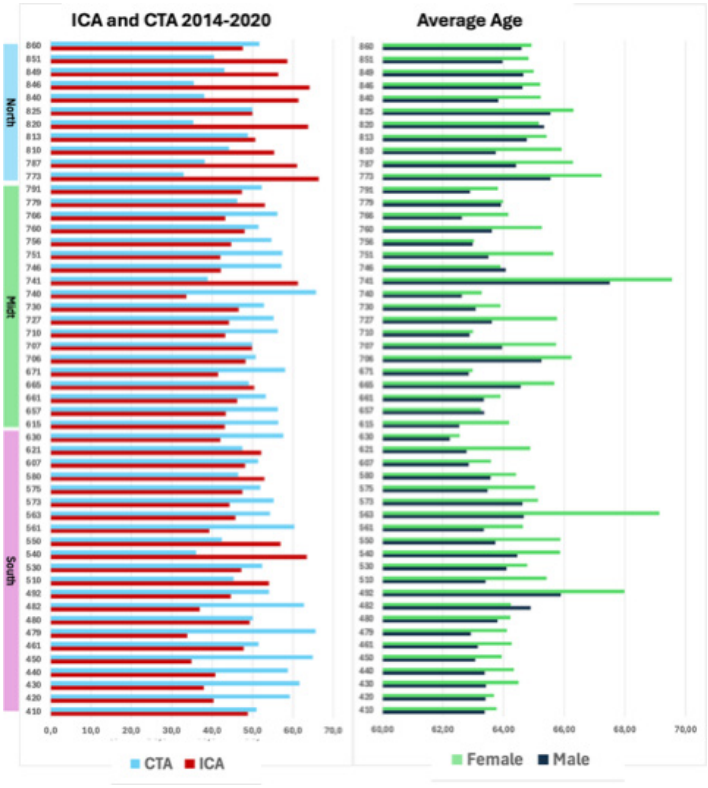

Figure 4: Fraction of ICA/CTA procedures (left panel) and average all patients (right panel) divided on municipality and sex. Significant difference in number of both procedure type and municipality ($p<0.001$; 2-way ANOVA) and age difference age both municipality and sex ($p<0.001$, 2-way ANOVA).

The initial change toward more use of CTA after the implementation in 2007 seems to continue with increasing CTA and falling ICA (Table 1). From 2014 to 2020, numbers of CTA increased by 28.6% and ICA was reduced by 29.1%. Overall, the diagnostic procedures were reduced by 3.2%, but more noticeable was a 7.7% reduction in invasive treatment within six months after diagnostic evaluation. The data further demonstrate a great difference in treatment fraction depending on primary procedure with 54.0% after ICA and 9.7% after CTA.

After diagnostic evaluation only, females had overall a lower mortality, while it was considerably higher than males in patients submitted to invasive treatment within the first six months and again with great differences between municipalities, especially in the treated group (Figure 5). The same pattern was seen after 30 days and 1 year (Table 2). When looking at mortality in relation to municipality inhabitants, the picture is slightly different. Despite the average higher female one-year mortality (4.68% vs. 2.83%), the impact on municipality mortality is less apparent at first glance, as the female mortality per 100,000 is lower than that of males in both diagnostic evaluation only and treatment groups (Figure 6).

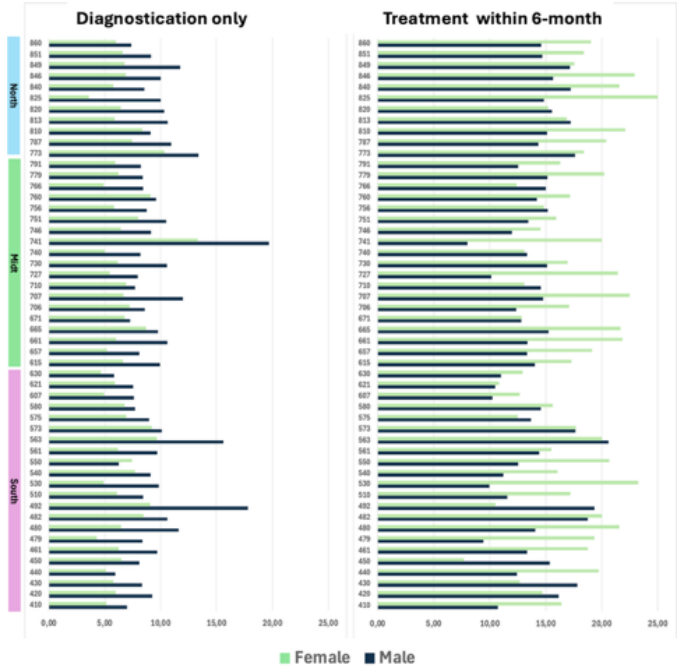

Figure 5: 5-year mortality of first-entry patients diagnostication only (left panel) or invasive treatment within 6 month (right panel) divided on municipality and sex. Females have higher mortality in treatment group and significant difference between municipalities ($p<0.001$, 2-way ANOVA). Females with lower mortality in diagnostication only group as well as difference between municipalities ($p<0.001$, 2-way ANOVA).

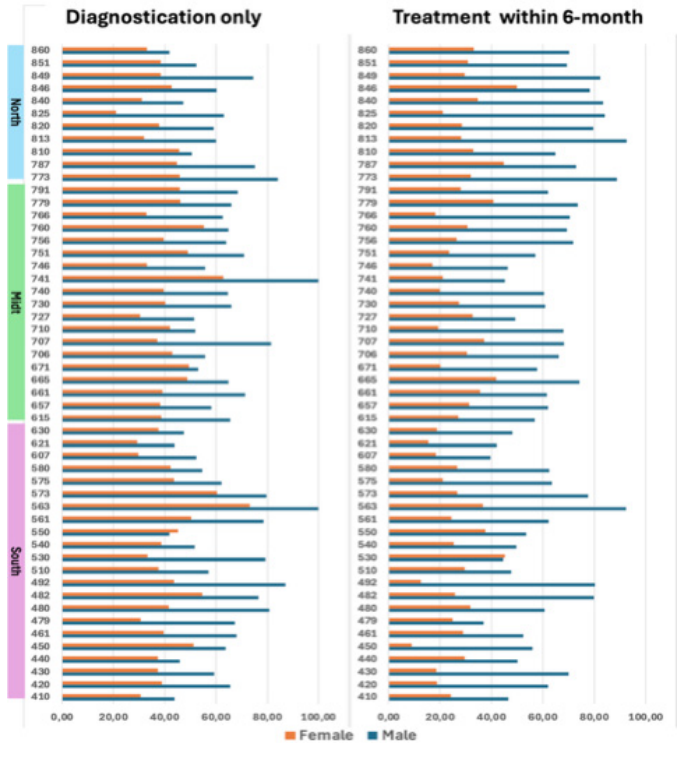

Figure 6: The 5-year mortality per 100,000 inhabitants and diagnostication only (left panel) and invasive treatment within 6 month (right panel) divided on municipality and sex. Both groups female number are lower than males and significant differences between municipalities ($p<0.001$, 2-way ANOVA).

Table 1: Number of diagnostic procedures and following treatment within 6 month divided on procedure type and year. Difference over years significant difference (p<0.001; ANOVA).

Procedure	2014	2015	2016	2017	2018	2019	2020
Invasive coronary angiography							
No	8370	8132	8006	7615	6851	6560	5932
Treatment %	50,4%	52,4%	51,8%	55,4%	55,5%	57,1%	57,0%
Computed tomography angiography							
No	6820	7521	8148	8462	8428	8540	8769
Treatment %	7,6%	8,3%	9,1%	9,7%	10,4%	11,1%	11,2%
All diagnostic procedures							
No	15190	15653	16154	16077	15279	15100	14701
Treatment %	31,2%	31,2%	30,2%	31,4%	30,6%	31,1%	29,7%

Table 2: Mortality divided on procedures and per 100,000 inhabitants divided on regions and sexes. Statistics: [#)] Two-way ANOVA; [*)] Independent t-test; [1)] One-way ANOVA.

Mortality	Sex	Diagnostic				Treatment < 6 month			
Mortality and procedures									
Region		**North**	**Midt**	**South**	*p-value*	**North**	**Midt**	**South**	*p-value*
30-days	**Male**	1,87	1,56	1,26	*0.001*	3,94	3,04	2,64	*0.001*
	Female	1,07	0,98	0,88		4,73	4,06	3,14	
	p-value	*<0.001*				*<0.001*			
1-year	**Male**	4,09	3,83	3,42	*<0.001*	7,72	5,72	5,51	*<0.001*
	Female	2,61	2,44	2,31		8,69	8,18	6,84	
	p-value	*0.017*				*<0.001*			
5-years	**Male**	9,79	9,36	8,55	*<0.001*	15,55	13,64	13,04	*<0.001*
	Female	6,71	6,59	6,11		19,00	16,87	16,03	
	p-value	*0.001*				*<0.001*			
Mortality per 100,000 inhabitants									
30-days	**Male**	11,0	10,9	9,0	*0.008*	19,2	13,7	11,0	*<0.001*
	Female	6,1	6,4	5,8		8,3	6,5	4,8	
	p-value	*0.007*				*0.012*			
1-year	**Male**	24,0	26,8	24,4	*0.022*	37,7	25,8	22,9	*<0.001*
	Female	14,8	15,9	15,2		15,3	13,0	10,4	
	p-value	*0.663*				*0.001*			
5-years	**Male**	57,4	65,3	61,0	*<0.001*	76,0	61,6	54,2	*0.001*
	Female	38,1	42,9	40,1		33,4	26,8	24,4	
	p-value	*0.638*				*0.048*			

Discussion

The important finding of this large, registry-based study of 110,199 patients was, as shown before, the overall lower female rate of invasive treatment, but also the huge difference in cardiac treatment between regions and municipalities. The findings agree with earlier studies handling different aspects of treatment of CVD patients [11,17,18], but the large inter-municipality differences of closely situated communities are more surprising and less readily explained. Some of the municipalities, especially islands dependent on ferry transport, are very small and few more or less patients may have great impact on the numbers. However, when excluding those with less than 5,000 inhabitants from the analysis, the picture becomes more uniform, but still with substantial variance, as the highest treatment fraction is 40% higher than the lowest in males, and 87% higher in females.

Another important observation is the apparent disconnection between the numbers referred to diagnostic evaluation and following treatment within six months. Even if the use of CTA has spread to other indications than the initial IHD, the invasive treatment or cardiac surgery is much more often from a primary procedure being ICA compared to CTA (ICA 54.0% vs. CTA 9.7%). Use of CTA has increased by 28.5%, while ICA with 29.1% has decreased marginally more.

However, some consider the specificity of CTA in diagnosing obstructive CAD as suboptimal, and a concern has been raised that the immense increase of CTA during the last decade and continued during the study period might result in increased cost and downstream ICA use and following treatments, due to falsely positive CTA procedures [1,19-22]. The major increase in CTA seems to be other than originally expected chronic coronary disease (CCS), but added arrhythmias and cardiomyopathies, with fewer possibilities of invasive treatments [2], which partly can explain the falling number of invasive treatments.

Previous studies have shown that female CVD is recognised later [23] and that females are less likely to be referred for testing [24] and that females consistently experience delays in guideline-directed therapy [25-27], altogether ending up with lower female referral to investigation and treatment than men. Nevertheless, the female fraction of all first-entry procedures in this study was 42.4%, matching their prevalence of CVD, and although it has been shown that female patients are investigated with CTA more frequently than males [28], we found a slightly different approach with overall female fractions of 34.7 % in ICA and 49.5% in CTA. Though, in agreement was found during the first three study years, the female fraction has gradually declined to 47.5% in the last two years. The different fractions of CTA and ICA likely result in an approach in which females are very underrepresented in invasive treatments but almost alike in patients with diagnostic evaluation only, and the differences between municipalities (Figure 3) seem more related to total numbers than to differences between procedure types or driven by the service in nearby hospitals.

Previous studies have advocated that CV hits females 7-10 years later than males [29,30] and was previously considered a similar entity with just a decade delay and thus an inborn risk of underestimating sex-specific differences [31,32]. In previous studies [8,15,17] we demonstrated a lowering age difference over the last two decades, which in the actual study has further declined to 1.0 years.

In a previous study we found geographical differences in PCI rates after acute coronary syndrome (ACS) or revascularization, indicating major differences between municipalities in the frequency of IHD [5,6]. In this study we have focused on overall outcome and not indications, but the previously observed differences in ACS and PCI might impact the municipality mortality differences.

Contrary to expectations following uniform efforts, females with IHD experience higher mortality than males [7,9,10]. The suggested reasons are more complicated and non-elective presentations with poorer outcomes [8,17,33,34], predisposition to suboptimal revascularisation [35], and a lower referral rate, likely resulting in more unfavourable pre-procedural baseline characteristics [36] all resulting in lower referral and following treatment as found in this study.

In agreement with earlier studies [7-10], 30-day, 1-year, and 5-year mortality was lower than males following invasive cardiac treatments (Figure 5). The interesting finding was the enormous differences between both regions and municipalities (Table 2), but although the mortality in females was higher in the treatment group, the impact on the inhabitants was masked by the much lower referral rate in females (Figure 6). All treatments are carried out in the three public fully tax-paid cardiac centres with uniform education and common staff exchange, so the regional differences are likely not policy-directed but due to local conditions, not easily explained in a small country and especially not on the municipality level. The missing impact in diagnostic evaluation only patients with no difference between regions in 1- and 5-year mortality does not clarify regional or local impact on health status.

Strengths and Limitations

A key advantage of this study is its large, representative cohort from the WDHR with 110,199 supporting the analyses and trustworthiness of the findings. The essential strengths are the mandatory and obligatory nature of the data, predominatly registered prospectively from a well-defined uptake area into a shared database used by all relevant institutions. The detailed in-hospital outcome and complete mortality follow-up on all patients undergoing invasive cardiologic and cardiac surgery procedures for more than two decades allows robust estimations of patients, results, and adverse events.

Nonetheless, the study carries inherent limitations, and especially the non-randomized nature may mask additional effects of missing covariates and potentially increase confounding. In a relatively uniform country with free tax-supported medical treatment and a fully developed ambulance and helicopter service, both acute and elective patients are presumed to receive the same treatment regardless of residence. Therefore, patient referral to diagnostic evaluation must be a valuable indicator of CVD, and any geographical differences are supposed to reflect the area prevalence and frequency of CVD, although local capability and focus may result in minor variations.

Conclusion

The initiative to increase investigation and intervention in CVD during the last decades has proven effective with the falling incidence of new cardiovascular diseases. The augmented screening by CTA has likely resulted in improved and faster access to treatment, but females are still referred less often than males for investigation and higher mortality following treatments remains. The major differences between regions and municipalities are not readily explained.

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