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Confounding factors of cardiovascular disease's mortality gender differences in Rwanda: An observational cohort study

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Abstract

Background: Cardiovascular disease (CVD) is still the leading cause of death in Rwanda, killing both men and women. The significant difference in mortality between male and female is perhaps the most notable feature of Rwanda's CVD epidemic. This study aimed at assessing the confounding factors of cardiovascular disease (CVD) mortality gender difference through the Mantel Haenszel Test for stratification.

Methods: We used data on mortality from 2018 to 2020 in Rwanda, as produced by Vital Statistics Reports through Civil Registration and Vital Statistics System (CRVS) and Health

Management Information System (HMIS). We computed the Mantel Haenszel Test for stratification to identify the confounders of the death of CVD gender difference.

Results: Based on the data provided, the study revealed that the main confounders of gender-specific death rates related to cardiovascular disease were age and place of residence. The unstratified and stratified effect estimates for confounding effect of age (RR=1.236 and RR_{MH}=1.13) and (RR=1.236 and RR_{MH} =1.110) for confounding effect of the place of residence.

Conclusion: Women have a higher relative risk of death as a result of their age and place of residence than men. The difference is greater among people stratified by place of residence than among people stratified by age. This is important to remember when investigating CVD risk factors in the population and developing a CVD prevention strategy, particularly in the female population, the focus will be based on age and place of residence as confounding factors.

Key words: Confounding effects, Death, Cardiovascular disease, Gender

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INTRODUCTION

Chronic non-communicable diseases (NCDs), particularly cardiovascular disease (CVD), diabetes, respiratory conditions, cancers, and neurological disorders, are among the leading causes of death and disability in both developed and developing countries. Developing countries account for more than 80% of the global CVD burden (Yach et al, 2005).

For the past decades, public health in Sub-Saharan Africa (SSA) has been focused on communicable diseases. With the arrival of HIV/AIDS, this image of infections as the primary health burden in SSA was reinforced. However, NCDs, including cardiovascular diseases, are becoming major causes of morbidity and mortality, and are expected to overtake infectious diseases by 2030(Yach et al, 2005; Mathers et al, 2006).

According to the World Health Organization (WHO), the number of deaths from cardiovascular disease in Africa will more than double by 2030 (GA, 2008). This double burden of disease could have a devastating impact on a continent already suffering from significant resource constraints, emphasizing the region's urgent need for appropriate interventions. However, it is

critical to have a thorough understanding of the potential confounding effects of cardiovascular disease (CVD) (Nyirenda et al, 2016).

Cardiovascular disease (CVD) is the leading cause of death and disability in the majority of developed countries for both sex. Medication, surgery, and other tertiary preventive measures may have reduced the lethality of CVD (Olav Axelson, 1978; Klag et al, 1996; Perry et al, 1995; Hsu et al, 2005; O'Seaghdha et al, 2009). The causes of CVD are multifactorial, and it has been discovered in the last decade that socioeconomic factors such as gender, age, and income level also contribute to the aetiology of CVD (Jvnstensen, 1989; Kristensen, 1989). However, the impact of these factors on the outcome is limited in terms of morbidity and mortality.

In Germany, women live longer than men and develop cardiovascular disease (CVD) at a later age. Metabolic syndrome is a major risk factor for CVD development, and gender differences in this syndrome may contribute to CVD gender differences. The contributions of the various components of metabolic syndrome vary by gender and by country (Crepaldi et al, 1979).

Rwanda, like other developing countries, is experiencing an increase in gender disparities with regard to deaths caused by cardiovascular diseases (Ministry of Health, 2016). However, little is known about the confounding factors affecting gender difference in mortality and morbidity from cardiovascular diseases. To that end, we conducted a cohort study in Rwanda to find out the confounders of CVD death in gender groups, primarily age, and residence status.

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METHODOLOGY

Study design

This is an observational cohort study conducted in Rwanda reviewing CVD data from 2018 to 2020 In 1998, the Rwanda Ministry of Health (MoH) established a Health Management Information System (HMIS) to monitor and follow up the health-related data including those from cardiovascular disease (CVD) across the country. In 2016, the National Institute of Statistics established a computerized CRVS web-based program to avoid the scandal of invisibility, where people are born and die without leaving any trace in legal records or official statistics due to stagnate systems over the years. To strengthen Rwanda CRVS system with the objective of providing reliable, complete and timely vital statistics from births, death and cause of death for the entire country.

Study population and setting

The study population included all patients (CVD death and non-CVD death) within health facilities operating in Rwanda with a known enrolment date and who followed up between 2018 and 2020. Patients were divided into two groups according to the presence/absence of cardiovascular disease. Exposed patients were classified as seropositive for CVD death and the remaining patients were classified as seronegative for non-CVD deaths which are unexposed groups. Outcome of interest was mortality (death) of the patients disaggregated to sex. The study population is made of all selected patients dead or non-dead of CVD and who fulfil the inclusion criteria.

Data source

The data needed for this work were collected through Civil Registration and Vital Statistics System (CRVS) and Health Management Information (HMIS) from the Ministry of Health and National Institute of Statistics of Rwanda (NISR, 2019; NISR, 2020). This study used data from an electronic medical record system that captures demographic and clinical characteristics at enrolment and longitudinal CVD clinical factors and vital statistics. This electronic database began collecting data prospectively in 2016.

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Study Quality Assessment

The quality of study was assessed using the Newcastle- Ottawa Scale for cohort studies. The gold standards for the 8 criteria will be as follows: (1) the exposed cohort was selected from the general population of CVD; (2) the non-exposed group was selected from the same population without CVD; (3) exposure was ascertained by the reliable way, with the *International Classification of Diseases* (*ICD*) codes; (4) excluded the ones who had CVD of interest before or at the start of study; (5) confounders were accounted for; (6) outcomes were assessed prospectively or through record linkage; (7) the follow- up time was long enough for outcomes to occur; (8) describing the loss of follow- up as missing values.

Statistical Analysis

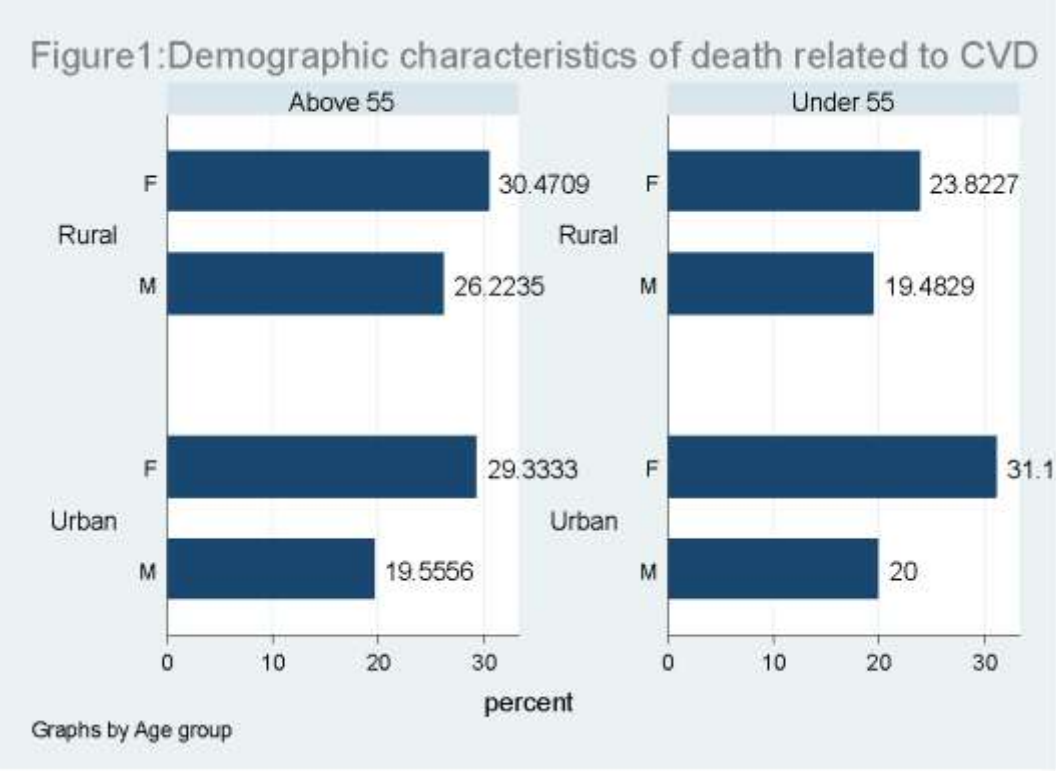
Stratification is the simplest method to control confounding during data analysis and represents the preliminary step for applying the Mantel-Haenszel formula. In general terms we have:

	yes	*no*	*total*
yes	a_i	b_i	N_{1i}
no	c_i	d_i	N_{0i}
total	m_{1i}	m_{0i}	n_i

$$\mathrm{RR}_{\text{Mantel-Haenszel}} = \frac{\sum_{i=1}^{s} \frac{a_i n_{0i}}{n_i}}{\sum_{i=1}^{s} \frac{c_i n_{1i}}{n_i}}, \quad \textit{for strata } i : \textit{from } 1 \textit{ to } s$$

The Mantel-Haenszel formula allows to calculate an overall, unconfounded, that is adjusted, effect estimate of a given exposure for a specific disease/outcome by combining (pooling) stratum-specific relative risks (RR). Using STATA version 13.0, stratum-specific RRs are calculated within each stratum of the confounding variable and compared with the corresponding effect estimates in the whole group (that is, with unstratified RR). When the effect estimates are roughly homogenous across strata and do not differ from that in the whole group, there is no confounding. Vice versa, when the effect estimates are substantially similar across strata but differ from that in the whole group, confounding is present (Maldonado et al, 1993).

RESULTS



According to the statistical analysis, for the three years 2018-2020, rural areas had consistently higher death rates related to Cardiovascular Disease than non-rural areas based on age subgroups (56.6 percent for rural and 48.8 percent for urban) for people over the age of 55, while rural areas had lower death rates related to Cardiovascular Disease than non-rural areas (43.2 percent for rural and 51.1 percent for urban) for people under the age of 55. Looking at the data in this graph, women were more likely to die than men in each region (54.2 percent for females and 45.8 percent for males) in rural areas and (60.4 percent for females and 39.6 percent for males) in urban areas.

	Death by sex		
CVD	F	M	Total
Positive	724	584	1308
Negative	5351	6598	11949
Total	6075	7182	13257

Relative Risk (RR) without stratifying

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                Point estimate      [95% Conf. Interval]
   ------------------------+------------------------
Risk difference .0378626        .0275507    .0481745
Risk ratio      1.236026        1.1727049   1.302765
+-------------------------------------------------
chi2(1) =    53.05  Pr>chi2 = 0.0000
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The hypotheses stated that Ho=RR=1.0 (there is no difference in risk between exposed and unexposed to the risk factor) and H1=RR≠1.0 (there is difference in risk between exposed and unexposed to the risk factor. Female deaths were significantly higher in seropositive patients than in seronegative patients. The RR of female death (i.e., the ratio of female deaths in seropositive versus seronegative patients) was 1.236, indicating that female patients with CVD had a significantly higher risk of mortality when compared to male patients (excess risk: +23.6 percent, 95 percent CI: 1.17–1.30). The chi square test for trend shows that CVD has an effect on gender death (P-value=0.000). If Gender is causally involved in patients' high risk of CVD mortality, the relationship between CVD and sex-specific mortality should be independent of other risk factors. Let us see it by using the RR with stratifying by age and residence.

Relative Risk (RR) with stratifying by age

CVD	Under 55		Total	Aged or Above 55		Total
	F	M		F	M	
Positive	396	328	724	328	256	584
Negative	1676	1330	3006	3675	5268	8943
Grand Total	2072	1658	3730	4003	5524	9527

Age group	RR	[95% Conf. Interval]	
Under 55	0.98100581	0.91144	1.05587
Aged or Above 55	1.36674308	1.26693	1.474410
Crude	1.236026	1.1727049	1.302765
M-H combined	1.138831	1 .1371012	1.312255

The sex-specific mortality were grouped into two age category; those who were aged 55 or above (Aged or above 55) and those who were under 55. The analysis of data stratified by age reveals that: a) there is significant excess risk of female death associated with Cardio Vascular Disease in both age category (95 percent CIs include one); b) the RR of female death was homogeneous across strata (RR = 0.98 for patients aged under 55 years and RR = 1.36 for those aged or above 55 years); and c) the unstratified and stratified effect estimates differ by more than 10% (RR=1.236 and RR_{MH}=1.13). These findings clearly show that the apparent strong link between CVD and sex-specific mortality that emerged in the unstratified analysis (RR = 1.236, 95 percent CI: 1.17–1.30) was due to the confounding effect of age.

Relative Risk (RR) with stratifying by residence status

CVD	Rural		Total	Urban		Total
	F	M		F	M	
Positive	588	495	1083	136	89	225
Negative	3780	3207	6987	1571	3391	4962
Grand Total	4368	3702	8070	1707	3480	5187

Residence status	RR	[95% Conf. Interval]	
Rural	1.00357	0.946300	1.0643060
Urban	1.90913	1.704578	2.1382423

Crude	1.236026	1.1727049	1.302765
M-H combined	1.110814	1.266695	1.487723

The sex-specific mortality were grouped into two residential area; those who resided in rural area and urban area. Data analysis stratified by residence status showed that: a) There is significant excess risk of female death associated with Cardio Vascular Disease in both rural and urban areas (95 percent CIs include 1); b) the RR of female death was homogeneous across strata (RR = 1.003 for patients living in rural areas and RR = 1.90 for those living in urban areas); and c) the unstratified and stratified effect estimates differ by more than 10% (RR=1.236 and RRMH=1.110). These findings clearly show that the apparent strong link between Cardiovascular Disease and sex-specific mortality found in the unstratified analysis (RR = 1.236, 95 percent CI: 1.17–1.30) was due to the confounding effect of residence status.

DISCUSSION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide and in low- and middle-income countries (World Health Organization, 2017; Collaborators et al,2015; Bovet et al, 2012; Roth et al,2015; Institute of Medecine, 2010; Fields et al, 2004). When compared to other world regions, Rwanda has a disproportionate burden of sex, age, and residence-specific death from cardiovascular disease (CVD) (Investigators et al, 2017; World Health Organization, 2018).

In this study, we investigated confounding effects of CVD gender difference' death focusing only on the age and the place of residence. Based on the data provided, our findings show that the main confounders of sex-specific death rates related to cardiovascular disease were age and place of residence.

According to the 2015 STEPS NCD (Stepwise Approach to Surveillance of Noncommunicable Diseases) risk survey, the overall prevalence of CVD was 15% for those aged 15 to 64 years; prevalence increased with age, reaching 39% for those aged 55 to 64 years; and CVD was the third leading cause of death in Rwanda (Ana A et al, 2019). Furthermore, Krisztina and el studied Health Disparities in Ischaemic Heart Disease Mortality in Hungary from 1970 to 2010. They discovered that age-adjusted IHD mortality rates for men and women increased from 1970

to 1993 and 1980 to 1999, respectively, before declining for both sexes. Age had a greater impact on mortality rates in women than in men (Krisztina et al, 2015).

Similarly, a study conducted in Japan that examined the mortality of heart disease (HD), ischemic heart disease (IHD) and cerebrovascular disease (CeVD) through an age-period-cohort (APC) analysis found that the period effects for all diseases decreased for both men and women during the studied periods. For all types of cardiovascular diseases, the cohort effects for men increased significantly from around 1940 to the 1970s. For both men and women, the cohort effects of HD decreased in cohorts born in the 1970s or later. However, in terms of IHD, the effects for women showed a steadily increasing trend in cohorts born in the 1960s or late (T O, 2020).

Payam Kabiri and el examined the impact of gender and place of residence on cardiovascular disease (CVD) events and related risk factors in the isfahan cohort study. Their study's findings revealed differences in CVD affecting the occurrence of sex-specific death based on place of residence (Kabiri, 2012; Antonio et al, 2012) . These findings are consistent with previous research (Antonio et al, 2012). Furthermore, preliminary findings from a similar cardiovascular disease assessment among rural populations revealed that some CVD risk factors, such as hypertension and abdominal obesity, were found to be associated with gender. When compared to men, women are more likely to be prevalent (Glushkov, 2019).

Study limitations.

As with most cohort studies, there was a significant loss-to-follow-up due to missing data for community and some health centre deaths. However, the significance of differences was not at the level that could severely affect the internal validity of the study. Despite the fact that all deaths in the community and other health centres were far from the scope of this study. As a result, risk factor patterns for CVD and sex-specific death may differ depending on where you live and your age.

In conclusion, women have higher absolute risks of death from CVD than men, with regard to where they live or their age. The difference is greater among people stratified by place of residence than among people stratified by age. Women have a higher relative risk of death as a result of their age and place of residence than men. This is important to remember when

investigating CVD risk factors in the population and developing a CVD prevention strategy, particularly in the female population, the focus will be based on age and place of residence as confounding factors.

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