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Impact of hypertension on mortality in adults in Moramanga, Madagascar: a retrospective cohort study in the community

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Abstract

Background Hypertension remains a global public health problem. This study aimed to evaluate the impact of hypertension on premature mortality among people living in Moramanga, Madagascar.

Methods Three communes of Moramanga district have been monitored since 2012 as part of the MHURAM project (Moramanga Health Survey in Urban and Rural Areas in Madagascar). In 2013, individuals aged 15 years and above were surveyed to estimate the prevalence of hypertension and identify risk factors. A follow-up survey was conducted in 2016–2017 to record deaths; causes of death were assessed through verbal autopsy (VA). The occurrence of premature death was evaluated using a retrospective cohort study design applied to data collected from adults aged 30 to 70 who participated in the hypertension survey. Mortality rates and partial life expectancy by sex and hypertension status were estimated using survival analysis; covariates associated with premature risk of mortality were identified using a Cox proportional hazards model. The contribution of causes of death to the difference in partial life expectancy between hypertensive and non-hypertensive individuals was evaluated using a decomposition analysis.

Results There were 4,472 participants in the hypertension survey aged between 30 and 70 during the follow-up. The average follow-up was 2.7 years per individual, resulting in 11,892 person-years in total with 117 deaths reported giving a mortality rate of 9.8‰ (13.1‰ for males and 7.1‰ for females). An estimated 3.2 years of life was lost among those diagnosed with hypertension compared to normotensive (32.0 years and 35.2 years respectively). Adjusted for gender, smoking habit, sedentary lifestyle, and wealth index, hypertension is a risk factor for premature death [HR = 1.58 95%CI (1.07–2.36)]. Hypertensive individuals also experienced higher all-cause and communicable disease mortality in people aged between 30 and 39 years.

Conclusion Hypertension is associated with higher risks of premature death in the community of Moramanga. In addition, hypertension contributes not only to mortality via cardiovascular diseases, but also through all causes combined. The health system should enhance prevention efforts, particularly for young hypertensive patients, when risk is most pronounced.

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Introduction

In the past 30 years, the total number of people aged 30–79 years diagnosed with hypertension (HT) has doubled from 331 million women and 317 million men in 1990 to 626 million women and 652 million men in 2019 [1]. Hypertension, defined as systolic blood pressure (BP) value ≥ 140mmHg and/or the diastolic blood pressure value ≥ 90mmHg in individuals 18 years and above [2, 3], is one of the most important risk factors for cardiovascular diseases (CVD) such as ischemic heart disease, stroke, and chronic kidney diseases leading to end-stage renal disease [4, 5]. In 2015, HT was a major disease burden globally, responsible for the loss of 143 million disability-adjusted life years (DALYs) worldwide [6]. Without appropriate measures and treatment, HT can be a leading cause of premature death i.e. before the age of 70. The mortality gap between hypertensive and normotensive individuals has been documented, showing that it remains relatively constant, even in high income countries where HT can be controlled through pharmacological and lifestyle interventions. The all-cause mortality rate among hypertensive adults is higher than in non-hypertensive persons [7]. Moreover, the risks of CVD and all-cause mortality were significantly higher in persons whose hypertension onset age was younger than 45 years [8].

An increase in deaths attributable to HT has been documented in the past 30 years mainly in East, South, and Southeast Asia as well as sub-Saharan Africa [2]. In sub-Saharan Africa, a lack of information on total- and cause-specific mortality and morbidity may further conceal the real picture. Very few African countries have a system of civil registration of vital events that meets international standards [9]. Less than half of all deaths are registered, and causes of death are rarely established [10] apart from some specific areas such as Health and Demographic Surveillance System (HDSS) sites [11, 12] or big cities where deaths are registered, i.e. Antananarivo, the capital of Madagascar [13]. Even rarer are data combining precise morbidity and mortality information related to the population. In Madagascar, apart from Antananarivo and few other main cities, civil registration and vital statistics systems and associated knowledge of cause-specific mortality are lacking - deaths occurring in the community are only certified by medical doctors in the main cities [14].

Since 2012, the Institut Pasteur of Madagascar has been monitoring the entire population of three communes of Moramanga district located in the Alaotra Mangoro region at 110 km from the East of the capital: the Moramanga Health survey in Urban and Rural Areas in Madagascar (MHURAM project) [15]. The district is home to several diseases that are health problems in Madagascar such as leptospirosis [16, 17], plague [18], malaria [19], rabies [20], and diarrhea in children especially those living in rural areas [21]. Moramanga spans a vast geographical district, including easily accessible as well as highly remote locations which provide a useful lens into the population's healthcare-seeking behavior. The location and socio-demographic profile of the population suggested that the areas could be representative of the island.

The cohort, initially designed as an HDSS, aims to fill the gap in health and mortality surveillance for communicable and non-communicable diseases (NCDs) outside of the capital city of Madagascar. In 2013, within the initial census, a study was conducted in adults aged 15 years and older to estimate the prevalence of hypertension and identify its risk factors [22]. Since 2014, deaths have been collected and causes of death assessed through the verbal autopsy (VA) method [23], as only deaths occurring in the health facility and in hospital are certified by medical doctors. In 2016, the yearbook of health sector statistics for Madagascar, which provides information on the state of health of the population (morbidity and mortality) and the curative and preventive activities of health facilities, reported that in the Alaotra Mangoro region, neonatal deaths among birth attended in health facilities were 0.4%, maternal deaths accounted for 0.92% of deliveries in district hospitals, and the specific lethality due to malaria was 10.4% among hospitalized malaria cases. Information for the country as a whole is not available [24].

Given the lack of resources for identifying the causes of death in the community, the MHURAM project addresses an important knowledge gap, opening the way to identifying the obstacles to the early detection and management of diseases in order to propose effective strategies in low-resource settings, especially in Africa.

In this study, we focus on the impact of hypertension on premature deaths in the cohort. We hypothesize that having HT, a major risk of CVDs, has a large impact on premature mortality.

Methods

Study design, site and population

The MHURAM project is a prospective cohort study located in Moramanga district. It started with the initial census of the population in the study areas in 2012 followed by surveys updating demographic events every 2 years from 2014 [15].

Moramanga, a district extending over 9,336 km², is included in the Alaotra Mangoro region, one of

Madagascar's 22 regions. It is a crossroads between the capital and the largest port in eastern Madagascar located at the end of the 2nd national road (Fig. 1). The district comprises 21 communes divided into 175 'fokontany' (the smallest administrative entity in Madagascar, equivalent to a neighborhood). The Institut Pasteur of Madagascar has implemented several research projects in Moramanga district including MHURAM project.

From October 2012 to May 2014, an initial census of the population, that is part of the activities in MHURAM project, was conducted after mapping all the dwellings giving a total of 16,789 households and 71,587 inhabitants, representing 24% of the district population, covering one urban commune (13 "fokontany") and two rural ones (17 "fokontany"). These 3 communes were chosen in part to leverage an existing community-based longitudinal survey initiated in 2010 as part of the MHURAM project focused on diarrheal diseases in children [21]. The eligibility criteria for the cohort are households located in the 3 communes and whose members do not intend to leave the area at the time of the survey, and who have agreed to sign the consent form. In addition to information about household members' socio-demographic characteristics, date of birth, urban/rural residence and household assets were recorded in each household [15].

A comprehensive follow-up was conducted from July 2016 to December 2017 to update on all pregnancies, deaths, and in- and out-migration since the initial census. During the follow-up visit, all previously registered and new households were visited by local fieldworkers, who had been trained to use the same procedures as those of the initial census.

Hypertension-related data

In 2013, a study was conducted on a sample of adults aged 15 years and older to estimate the prevalence of hypertension and identify its risk factors, where candidates included history of blood pressure above 130mmHg for systolic blood pressure, family history of hypertension, recent weight gain, sedentary lifestyle, salt diet, smoking and alcoholic habit, and presence of suggestive signs (tinnitus, dizziness, waking headache, nosebleed)

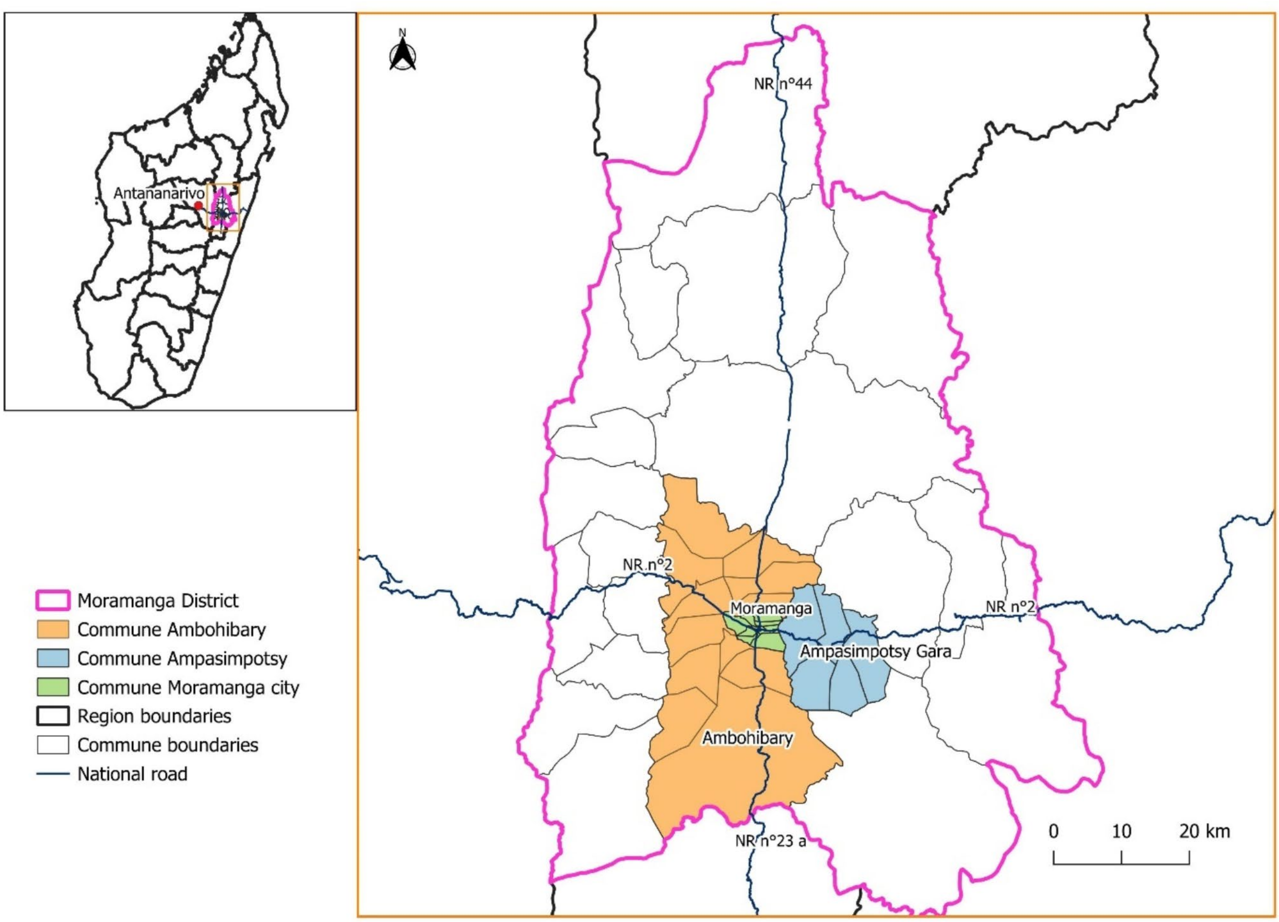

Fig. 1 Localization and catchment areas of Moramanga Health Survey in Urban and Rural Areas in Madagascar with national roads crossing the Moramanga district.
Source: Geographic Information System (GIS) team, Unité d'Épidémiologie et de Recherche clinique, Institut Pasteur de Madagascar

[22]. Sedentary lifestyle was assessed using the following question: 'Are you sedentary, that means you don't do any regular physical activity or sport?'. Consumption of tobacco and alcohol were assessed using the following questions: 'Do you regularly smoke?' and 'Do you drink alcohol regularly?'.

The sample consisted of all adults from 7 fokontany of the two rural communes and a random sampling of adults from the 13 fokontany in the urban commune. Height, weight and two blood pressure (BP) measurements, taken after 5 min of rest and at least 5 min apart, were collected with additional information on known risk factors of hypertension. In total, 7,262 adults aged 15 years and older participated in this hypertension survey. Hypertension was defined as mean systolic BP $\geq$ 140 mmHg or mean diastolic BP $\geq$ 90 mmHg [25] or self-reported use of antihypertensive medication prescribed by a physician within the four weeks preceding the study, verified from health booklets or the presence of drugs at the time of the survey. Data from the hypertension survey are provided in Ratovoson et al. published in 2015 [22].

Mortality data

All households where a death was reported between the initial census and the follow-up were revisited for verbal autopsy (VA) interviews to determine the causes of death. In contexts where medical certification is limited or unavailable, WHO recommends using VA methods to fill existing gaps and develop an overview of causes of death that can help to guide policy development, implementation and evaluation in health system [23, 26, 27]. Local trained fieldworkers conducted the VA using WHO instruments [23, 28] translated into Malagasy. Two physicians reviewed the completed questionnaires to determine the probable cause of death. In case of discordant results, a third physician reviewed the completed questionnaire to arbitrate between the two formerly suggested causes of death. If no consensus was reached by three blind reviewers, the cause of death was classified as 'undetermined' [29]. The probable cause was then coded using the International Classification of Diseases, 10th revision (ICD-10). Afterward, causes of death were grouped into four categories from the Global Health Observatory group of WHO [30]. The first group consisted of causes of death due to communicable, maternal causes and nutritional conditions; the second group involved CVD and diabetes; the third group was "other NCDs", and the fourth group "injuries and other external causes". A last group, called "unknown cause" covered ill-defined, undetermined events, as well as cases where verbal autopsies were not performed, because of a refusal, or because the household was absent or moved. The correspondence of the ICD-10 in each group is in supplementary files (Appendix 5).

Socio-economic data

The wealth index was assessed using a principal component analysis on the basis of each household's assets as described by Vyas and Kumaranayake [31]. First, a descriptive analysis of variables related to socio-economic level in the MHURAM initial census questionnaire was carried out to select variables that would be kept in the analysis. Categorial variables (such as type of floor or type of toilet) were recoded into binary variables to allow inclusion in the principal component analysis. Durable assets owned by less than 2% of households were excluded as well as variables with excessive missing values. In urban areas, housing characteristics (number of bedrooms, type of floor, lighting, fuel used for cooking, type of toilet, drinking water supply), household assets (possession of radio, television, mobile phone, fridge, sewing machine, motor vehicle), and possession of animals (chicken and dog) were included. In rural areas, the number of bedrooms, possession of farm animals (chicken, ducks, and cattle), and possession of land to cultivate (gardens, orchards) and carts were included. Coefficients were calculated by using the loading of the first principal component and scores were obtained on the coded value of each mentioned variable. The socio-economic score was then reclassified into 4 quartiles, analyzed separately for rural and urban communities. The wealthiest in the urban and the rural areas do not have the same wealth, but are in the 1st quartile of their respective area.

Statistical analysis

This study is based on data collected on adults aged 30 to 70 living in households enumerated both at the initial census and during the follow-up, who also participated in the hypertension survey. The outcome variables were the occurrence of death in the adult population; and we evaluated the impact of hypertension on the risk of premature death and on the probable cause of death. The exposure was the diagnosis of hypertension which was defined above.

We performed survival analyses to examine the relationship between a diagnosis of hypertension and individual survival. To estimate the risk of dying according to the age of the individuals, the survival function was calculated with the date of birth as the time of origin, left censored at either the time of the survey or the 30th birthday and right censored at either the time of the last interview or the 70th birthday, or out-migration for those lost to follow-up. For deceased participants, the duration of follow-up time lasted from the date of hypertension survey until the date of the death. Based on our data on follow-up time and deaths, we could estimate mortality rates, and the number of years lived on average between the ages of 30 and 70, i.e. partial life expectancy, for all individuals, by sex and hypertension status.

A Cox model analysis was performed to evaluate the association between covariates and the risk of dying from premature death i.e. before the age of 70. We aimed to estimate the impact of hypertension on the risk of dying adjusting for additional covariates (gender, rural/urban residence, wealth index, family history of hypertension, sedentary lifestyle, and smoking habit). The full model included covariates with a p-value less than 0.20 in bivariate analysis. Observations were there had missing data in the covariates were excluded. Schoenfeld residual analyses were performed to check the validity of the final model.

We then estimated the contribution of causes of death to the mortality gap between the two groups (hypertensive / non-hypertensive), looking at the difference of years lived on average by age groups 30–39; 40–49; 50–59; 60–69 and broad group of causes. These age stratifications are necessary so that the results (mortality rate, age pyramids) could be compared with other data. To do so, we used the Arriaga-Andreev-Pressat method [32, 33, 34].

Analyses were conducted using STATA software (version 17) [35] and the R statistical software (version 4.2.2) [36, 37].

Results

Descriptive analysis

The results of the hypertension survey showed a prevalence of 27.0% (95% CI: 25.6–28.5%) in rural areas and 29.7% (95% CI: 28.3–31.1%) in the urban areas of Moramanga. Among hypertensive individuals, only 1.7% in rural areas and 5.3% in urban areas were on antihypertensive treatment for at least 1 month before the survey [22]. Persons identified as hypertensive were advised on health and diet by the nurse in charge of the mobile clinic and were advised to consult their nearest health center.

From the sample of adults (15+) who participated in the hypertension survey ($n = 7{,}262$), 237 persons aged 70 years and over were excluded before the survey, as well as 2,553 persons below 30 years at the end of the follow-up, giving a total of 4,472 persons in the cohort i.e. from the date of the survey interview in 2013 to the date of the last interview during the round 2016–2017. There were more women (55%) than men (45%); 10% were below 30 years old at the time of the survey and therefore left censored in the survival analysis (before their 30th birthday). Most of the participants were in their thirties (38%) or forties (25%), while 19% were in their fifties and 8% older than 60. Less than half (48%) lived in a rural area. This subsample selected slightly richer individuals (54%) than in the original sample. More than a third (36%) of individuals were identified as hypertensive at the time of the survey, only a minority (8%) reported a sedentary lifestyle and 15% smoked (Table 1).

The survival analysis followed up an average 2.7 years per individual, resulting in a total 11,892 person-years

Table 1 Socio-demographic characteristics and risk factors of hypertension of the participants of the hypertension survey aged between 30 and 70 during the follow-up[(a)]

		No hypertension at the survey		Presence of hypertension at the survey		Total		
		N	**% (95%CI)**	***N***	**% (95%CI)**	***N***	**%**	**95% CI**
Gender	Male	1309	45.7 (43.8–47.5)	721	44.9 (42.4–47.3)	2030	45.4	43.9–46.7
Age group at the hypertension survey[(b)]	25–29	363	12.7 (11.5–13.9)	93	5.8 (4.7-7.0)	456	10.2	9.3–11.1
	30–39	1264	44.1 (42.3–45.9)	432	26.9 (24.8–29.1)	1696	37.9	36.5–39.3
	40–49	704	24.5 (23.0-26.2)	420	26.1 (24.1–28.3)	1124	25.1	23.9–26.4
	50–59	413	14.4 (13.2–15.7)	422	26.3 (24.2–28.5)	835	18.7	17.5–19.8
	60–69	122	4.2 (3.6-5.0))	239	14.9 (13.2–16.7)	361	8.1	7.3–8.9
Area of residence	Rural	1464	51.1 (49.2–52.9)	704	43.8 (41.1–46.3)	2168	48.5	47.0-49.9
Wealth index[(c)]	Poor	633	22.1 (20.6–23.6)	308	19.2 (17.3–21.2)	941	21.4	20.2–22.6
	Middle	709	24.7 (23.1–26.3)	385	24.0 (21.9–26.1)	1094	24.9	23.6–26.2
	Rich	718	25.0 (23.5–26.7)	444	27.6 (25.5–29.9)	1162	26.5	25.2–27.8
	Richest	755	26.3 (24.7–28.0)	439	27.3 (25.2–29.6)	1194	27.2	25.9–28.5
Sedentary lifestyle	Yes	204	7.1 (6.2–8.1)	142	8.8 (7.5–10.3)	346	7.7	7.0-8.6
Smoking habit	Yes	401	14.0 (12.8–15.3)	261	16.3 (14.5–18.1)	662	14.8	13.8–15.9
	Total	2866	64.1 (62.6–65.5)	1606	35.9 (34.5–37.3)	4472	100.0	

Notes: [(a)] from the date of the survey interview to the date of the last interview during the round 2016–2017; [(b)] individuals aged 25–29 at the time of the survey are left censored in the survival analysis until their 30th birthday; [(c)] Wealth index has missing values ($n = 81$). Source: MHURAM Project

Table 2 Survival data and mortality indicators related to the participants to the hypertension survey aged between 30 and 70 during the follow-up[(a)]

	Both sexes	Male	Female
Number of individuals	4472	2030	2442
Mean time under follow-up (years)	2.7	2.6	2.7
Total number of analysis time (person-years)	11892.0	5318.8	6573.2
Number of deaths	117	70	47
Mortality rate (per 1000)	9.8 (8.2–11.8)	13.1 (10.4–16.6)	7.1 (5.3–9.5)
Partial life expectancy between ages 30 and 70 (years)	34.2 (33.2–35.1)	32.6 (31.1–34.2)	35.5 (34.4–36.7)
among individuals with no hypertension	35.2 (34.0-36.4)	33.9 (32.0-35.8)	36.5 (35.1–38.0)
among individuals with hypertension	32.0 (30.0–34.0)	30.4 (27.2–33.6)	33.0 (30.2–35.9)

Note: [(a)] from the date of the survey interview to the date of the interview during the round 2016–2017. 95% Confidence intervals are provided in brackets. Source: MHURAM Project

Table 3 Cox hazard model on the risk of dying between 30 and 70 among the participants of the hypertension survey during the follow-up[(a)]

	Hazard ratio	*p* > z	95% Confidence Interval	Test of proportional-hazards assumption
Hypertension	1.58	0.023	(1.07–2.36)	0.038
Female vs. Male	0.64	0.029	(0.43–0.96)	0.757
Wealth index: 2nd quartile vs. 1st	0.94	0.819	(0.55–1.61)	0.902
Wealth index: 3rd quartile vs. 1st	0.99	0.958	(0.59–1.66)	0.836
Wealth index: 4th quartile vs. 1st	0.53	0.031	(0.29–0.94)	0.517
No sedentary lifestyle	0.37	0.000	(0.23–0.60)	0.477
No smoking habit	0.69	0.134	(0.42–1.12)	0.092

Note: [(a)] from the date of the interview to the date of the interview during the round 2016–2017; due to missing values for the wealth index, the model is conducted on 4,391 individuals (11,643 person-years and 115 deaths)

Source: MHURAM Project

between the age of 30 and the age of 70. During this follow-up, 117 deaths were reported resulting in a mortality rate of 9.8‰ (13.1‰ for males and 7.1‰ for females) (Table 2).

In the absence of death, participants aged 30 years would have lived 40 years between 30 and 70 but 6.8 years of life were lost due to premature mortality leading to a partial life expectancy estimated at 34.2 years for both sexes (32.6 and 35.5 for males and females respectively, a statistically significant difference). Individuals with hypertension are estimated to live on average 3.2 years less than those who were not hypertensive (32.0 years and 35.2 years respectively) and the number of years lost (3.5), is the same for males and females (Table 2).

Risk factors of premature death

The full Cox model included as covariates the presence of hypertension, gender, wealth index, smoking habit, and sedentary lifestyle. We thus excluded the area of residence and family history of hypertension because not significant in bivariate analysis. The analysis confirms that hypertension is a risk factor for premature death [Hazard ratio (HR) = 1.58 95%CI (1.07–2.36)] even after adjusting for gender (HR = 0.64 [CI95% (0.43–0.96)], females experience lower hazards than males), sedentary lifestyle (not being sedentary protect against premature death, with HR = 0.37 [CI95%(0.23–0.60)] and smoking habit (though for the latter, p-value = 13%) (Table 3). The model validity by Schoenfeld residual analyses shows that p-values are higher than 5% for all covariates except hypertension (Table 3). A visual check of the proportional-hazard assumption (Kaplan-Meier curves and Log-log plot) confirms that, though the risk of dying is always higher for hypertensive persons than for non-hypertensive persons, the hazard ratio seems to decrease over age and the difference is higher among younger people than among older ones (Appendix 1).

Contribution of the causes of death in the years of life lost among the group of hypertensive individuals

As noted in Table 2, we estimate that there are 3.2 years of life lost between individuals with hypertension and without from age 30 to age 70. Mortality rates shows more than double the mortality rate in the hypertensive group [15.5‰; 95CI (12.2‰-19.6‰)] than in

Table 4 Differences in the years of life lost among the group of hypertensive individuals between the ages of 30 and 70 years during the follow-up[(a)] compared to the group of non-hypertensive individuals, by age group and broad group of causes

	Communicable diseases	Cardiovascular diseases and diabetes	Other NCDs	External causes	Unknown cause	Total
30–39	-1.07	-0.18	0.07	-0.10	-0.55	-1.84
40–49	-0.07	-0.43	0.12	-0.21	-0.13	-0.72
50–59	-0.01	-0.19	0.06	-0.08	-0.25	-0.47
60–69	-0.01	-0.12	0.07	0.04	-0.16	-0.18
Total	-1.15	-0.92	0.31	-0.36	-1.09	-3.21

Notes: [(a)] from the date of the survey to the date of the interview during the round 2016–2017

Reading note: between the ages 30 and 70, hypertensive individuals lived 3.21 less than the non-hypertensive individuals on average (difference = -3.21): 1.07 years were lost because of deaths due to communicable diseases that occurred at ages 30–39

Source: MHURAM Project

non-hypertensive [6.5‰; 95%CI (4.9‰-8.6‰)], and also by age group (Appendix 2).

Regarding cause-specific mortality, for 99 out of 117 deaths, a probable cause of death was assigned after VA process: 13 causes were classified as communicable diseases, maternal mortality and malnutrition, 36 as cardiovascular diseases and diabetes, 29 in other NCDs group and 11 in injuries and other external causes. Finally, 10 deaths were classified as ill-defined and added to 18 deaths of unknown causes because VAs were not done.

Regarding cause of death distribution by hypertension status, hypertensive individuals experienced a higher all-cause mortality mainly in communicable diseases, maternal causes and malnutrition, and in cardiovascular diseases and diabetes (Appendix 3). Of the 13 deaths due to infectious diseases, maternal causes and malnutrition, nine were in hypertensive individuals, four of which were due to tuberculosis, three to pneumopathy, one to bacterial intestinal infection and one to puerperal infection. For non-hypertensive, three were due to pneumopathy and one to malaria.

The detailed decomposition of the difference between the partial life expectancies of the two groups is presented in Appendix 4. By age group, 1.8 years were lost between ages 30 and 39; 0.7 years between 40 and 49; 0.5 years between 50 and 59, and 0.2 years between 60 and 69. Regarding cause-specific mortality, leaving aside the group of other NCDs (which excludes cardiovascular diseases), communicable diseases were responsible for a loss of 1.1 year, cardiovascular diseases of 0.9 year lost, and injuries and other external causes for 0.4 year. Other NCD-related mortality was slightly higher in the non-hypertensive group and contributed to a 0.3-year difference. Finally, the cause of death was unknown for a quarter of deaths with a larger burden in the hypertensive group than in the non-hypertensive one.

Table 4 presents the differences, combining age group and sex. Almost all the loss of years due to communicable diseases, maternal cause and malnutrition affect the youngest ages [30, 31, 32, 33, 34, 35, 36, 37, 38, 39]; while years are lost because of cardiovascular deaths in all age groups. External mortality was also a bit higher among the hypertensive group, except for the oldest (60–69). Other NCD-related mortality was lower in all age groups.

Discussion

Our study demonstrates a considerable burden of premature death associated with hypertension among adults living in urban and rural areas in the Moramanga district. To our knowledge, it is the first study in Madagascar to analyze mortality and cause of death among adults outside the capital city. The mortality rate between 30 and 70 was estimated at 9.8‰ with 13.1‰ in males and 7.1‰ in females. During follow-up, about 7 years of life were lost due to premature deaths, and people diagnosed as hypertensive during the initial survey lost around three more years. After adjusting for gender, wealth index, risky habits, and behavior, hypertension remains a risk factor for premature death. In addition, hypertensive individuals experienced higher mortality, not only because of a higher cardiovascular mortality but also because of mortality due to communicable diseases.

The gender gap in partial life expectancy found in this cohort (approximately 3 years) is similar to the one estimated for life expectancy at age 30 using the national population census of Madagascar of 2018 (mean 43.9 years, 42.8 for males and 45.2 for females) [38]. For both sexes, the partial life expectancy is lower for individuals diagnosed with hypertension: males and females lose respectively 9.6 years and 7 years because of premature deaths occurring between the ages of 30 and 70. Studies have already shown that in women with hypertension, the burden of disease is lower than in men for all ages except over 75 years [6, 39]. Hypertension-related mortality depends primarily on cardiovascular diseases whether in high- or middle-income countries [6, 40, 41, 42, 43].

At the time of the hypertension survey, participants above 15 and below 50 years old represented 62% and 59% in the rural and urban areas respectively [22]. In some studies, patients diagnosed with hypertension at young adult ages were reported to develop target organ injuries such as ventricular hypertrophy, coronary calcification and diastolic dysfunction [44], kidney or cardiovascular event occurrence [41], and higher risk of kidney and cardiovascular related-mortality as well as higher overall mortality [8, 41]. In the absence of adequate treatment, as is generally the case in Madagascar and many low-income countries, these risks are likely to be exacerbated, leading to premature death.

During the survey, participants with hypertension were sensitized and referred to their nearest health centers. Literature on blood pressure reduction to prevent cardiovascular diseases and death revealed that a 10 mmHg reduction in systolic blood pressure in hypertensive patients could reduce the risk of stroke by 27%, the risk of developing heart failure by 28%, the risk of coronary heart disease by 25% and the risk of all-cause mortality by 13% [45]. In addition, Zhou D et al. described that disparities in cardiovascular or overall mortality between patients with and without hypertension vanish when focusing solely on patients with treated and well-controlled hypertension [46]. The premature mortality observed in the cohort suggests that some patients weren't compliant with provided dietary advice or periodic blood pressure checks at health centers. Non-adherence to treatment for chronic diseases such as hypertension remains a difficult problem worldwide. A study conducted in patients with epilepsy or hypertension in rural areas of Ethiopia revealed that patients suffering from these diseases declare that their health has improved, they no longer feel sick and therefore they do not come to medical consultations anymore, thus becoming lost to follow-up [47]. A meta-analysis of 25 studies in hypertensive adults from 15 countries found that non-adherence to antihypertensive treatment affected 45% of patients and 31% of patients with comorbidities. Interestingly, this meta-analysis also found that non-adherence was even higher (83.7%) in patients whose hypertension was not controlled [48].

Regarding causes of death, studies have already shown the association between the diagnosis of hypertension and cardiovascular or all-cause mortality in high and middle-income countries [6, 7, 8, 39, 40, 41, 42, 43], where the causes of death are predominantly NCDs. In low-income countries such as Madagascar, political instability and a weak healthcare system are contributing to a slowdown in the epidemiological transition and a cumulative burden of infectious and non-transmissible diseases [13]. An example is the association between tuberculosis and diabetes which was shown in a hospital located in Antananarivo: 20% of patients hospitalized for tuberculosis had been diagnosed as diabetic [49]. Furthermore, subclinical presentation with a significant biological inflammatory syndrome was more frequent in diabetic people [49]. In situations where it is difficult to seek care, this insidious development of tuberculosis could lead to a higher mortality rate. The cause of death among people aged 30–39 years in our cohort shows that hypertensive people died frequently from communicable diseases, especially tuberculosis. Some meta-analyses have suggested that diagnosis of tuberculosis is a marker for elevated risk of CVD [50] and a nationwide population-based cohort study reveals that tuberculosis patients are at higher risk of developing acute coronary syndrome, which can be a complication of hypertension [51]. In African populations, infectious diseases like tuberculosis remain a major cause of heart failure particularly in the context of HIV [52, 53]; tuberculosis can also lead to constrictive pericarditis [53]. A recent study conducted in Zambia and South Africa revealed that cardiac involvement is frequent in tuberculosis patients, especially in newly diagnosed young persons [54].

Faced with this situation of premature risk of death, where seeking care can be delayed for various reasons, one strategy in a resource-limited setting like Madagascar is task shifting. The involvement of community health workers (CHW) to strengthen the health system in the early detection of illnesses and in the adherence to treatment is needed [55]. Commitment from health system leadership, CHW training and support, regular engagement between CHWs and health providers, community partnerships will be essential for planning the implementation of community-based interventions [56].

Limitations

This study presents some limitations. First, partial life expectancy and cause-specific mortality estimates are based on low frequencies of deaths and years of follow-up. While the first analyses conducted (presented in Tables 2 and 3) accounts for uncertainty, decomposition by cause of death does not; because the method cannot provide confidence intervals, and results must be interpreted with caution (Table 4). Further years of observation are required to consolidate this result. At the time of the survey, information on hypertension status was communicated to the respondents, we can assume that some of them will seek care and treatment. If this had occurred, this hypertensive group would be potentially better treated than the general population, making them a biased community for the study of outcomes of hypertension in Madagascar more broadly. Without this bias, the difference in mortality between the two groups would have been even higher and our results, already significant, would be an underestimate of the burden of hypertension. Finally, the causal relationship between hypertension and higher risks of mortality, especially the non-cardiovascular related mortality must also be interpreted cautiously: does hypertension lead to a higher risk of overall mortality, including infectious diseases? Or is the group of young hypertensive individuals selected along some other axis, i.e. cumulating more unfavorable conditions or unhealthy behaviors? Even if, in the multivariate analysis, the risk of death remains higher after adjusting for wealth index and sedentary lifestyle, we cannot exclude other selection effects. However, this result is in line with the fact that NCDs and infectious diseases interact as the COVID-19 pandemic dramatically highlighted when people with CVD risk factors especially hypertension were clearly at higher risk of Covid-19 mortality than others. Further retrospective and prospective studies are needed to explore these interactions.

More generally, the VA method provides series of deaths by causes that we assume to be "probable". Causes of death are more or less easy to diagnose through this method, depending on their specificity and sensitivity [57]. For instance, injuries and epidemic diseases are easier to diagnose than non-communicable diseases with silent symptoms. However, it is supported by WHO in all contexts where there is no any alternative data such death certificates [26, 28, 29, 58].

Conclusion

Our results indicate that a diagnosis of hypertension is associated with premature death in urban and rural areas in Madagascar. The risk of premature death is higher when the individual's age at diagnosis is younger. Our results confirm the fact that the all-cause mortality rate among hypertensive adults is higher than in non-hypertensive persons. These results suggest that the health system should increase prevention measures in patients diagnosed with hypertension, not only in the elderly but also, and more importantly in younger hypertensive patients. Integrating CHWs into hypertension management could potentially improve health service access, with impacts on early detection and adherence to treatment.

Abbreviations

BP	Blood Pressure
CI	Confidence interval
CVD -	Cardiovascular diseases
COVID-1	Coronavirus disease 2019
DALYs	Disability adjusted life years
HR	Hazard Ratio
HT	Hypertension
ICD-10	International Classification of Diseases, 10th edition
MHURAM	Moramanga Health survey in Urban and Rural Areas, Madagascar
NCD	Non-Communicable Diseases
VA	Verbal Autopsy
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

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Author contributions

RR and GD designed this work and analyzed data. RM coordinated the data management. PR and AS determined the cause of death. RR and PP conceived the hypertension survey. RVR initiated the cohort project. RR and GD wrote the first draft of the manuscript. All authors reviewed the manuscript and approved its submission.

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Data availability

A standardized template for a data-sharing agreement is available in French and English version at IPM. The datasets used and analyzed during the current study are available from the corresponding author (rila@pasteur.mg) on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the World Medical Association Declaration of Helsinki for medical research involving human participants. The study was approved by the "Comité d'Ethique de la Recherche Biomédicale auprès du Ministère de la Santé Publique" (Biomedical Research Ethics Committee attached to the Ministry of Public Health; Approval N°52-CE/MINSAN 02 November 2009 and amendment N°60/MSANP/CE 26 May 2016 for MHURAM project and approval N°020-MSANP/CE 08 February 2013 for Hypertension study). During the initial census and the follow-up visit, informed consent was obtained from the head of the household participants included in the study. For hypertension survey, written informed consent was obtained from adult participants. For minors, written informed consent was obtained from parents or guardians on behalf of the minors enrolled in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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