Predictors of metabolic syndrome among people living with HIV in the Gedeo-Zone, Southern-Ethiopia: an unmatched case-control study

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Abstract

Background

Metabolic syndrome (MS) among people living with HIV (PLHIVs) is a global public health issue. However, there is no primary data about predictors of MS in the SSA and Ethiopia. Therefore, the aim of this study was to determine predictors of MS, among PLHIVs in the Gedeo-Zone, Southern-Ethiopia.

Methods

Unmatched case-control study approach, among PLHIVs who served at randomly chosen two hospitals and health centers in the zone, in between (December 29th-2017 and January 22nd-2019) was done. WHO-steps tools were used to gather the data, finally handled with (Epidata-V-3.1 and SPSS-V-22) software's. Lastly, using a multivariable conditional-LR-model, 4-models with AOR (95%CI) were computed to arrived at the final model, and then variables accepted as significant at (p-value < 0.05) level.

Result

Overall, 633 PLHIVs (139 cases and 494 controls) were included in the analysis. The leading factors associated with MS were Age(≥ 45 years-old) (AOR=4.0, 95%CI: 1.4-11.9), completed secondary school education (AOR=0.1, 95% CI: 0.01-0.5), un-employed (a home-maker AOR=0.1, 95%CI: 0.03-0.7 vs able to work AOR=0.1, 95%CI: 0.06-0.5), Antiretroviral-therapy-exposed (AOR=0.1, 95%CI: 1.0-8.5), WHO-stage ($\geq$ III) (AOR=4.4, 95% CI: 1.4-13.4), total physically activity (AOR=0.1, 95% CI: 0.04- 0.35), history of blood sugar measured (AOR=10.7, 95%CI: 3.3-34.6), elevated waist-circumference (AOR=6.9, 95%CI: 2.5-18.7), raised body mass index (AOR=5.4 95% CI: 1.6, 18.4), fasting-glucose (AOR=29.3, 95%CI: 10.0-85.4), raised triglyceride (AOR=4.8, 95%CI: 2.0-11.3), and low high density lipoprotein (AOR=12.3 95% CI: 5.2, 29.3).

Conclusion

The finding implicated, the significance of planning intervention actions that targets the above factors in to account.

1. Background

Over the 3/4th of global NCDs deaths, 30.7 million occurred in low and middle-income countries (LMIC), with about 48% of deaths in these countries occurring before the age of 70, in 2015 [1-3]. In the Sub-Saharan Africa (SSA) region, over the next two decades, it is expected to escalate substantially [2]. In Ethiopia, it is estimated to account for 30% of total deaths, with 9% and 1% proportional mortality from CVDs and Diabetes, respectively [3].

Following the global implementation of highly active antiretroviral treatment (HAART), there achieved the reduction of 30 million new infections and nearly 8 million Acquired Immune Disease Syndrome (AIDS)

associated deaths [2, 4], and increase in life expectancy of people living with HIV (PLWH) worldwide. However, apart from the success achieved, works of the literature disclosed that antiretroviral therapy (ART) has contributed to forming an aging people living longer with the treatment, and thus to be at risk of developing Non-communicable disease (NCD)[2, 4-10]. With this reasons, the HIV infection environment nowadays represented as a typical illustration of the interaction between infectious diseases and non-communicable diseases (NCDs) [2, 4, 11-13].

Metabolic syndrome (MS) is the risk markers of NCDs, usually diagnosed based on the following medical conditions: abdominal obesity, elevated blood pressure (BP), elevated fasting plasma glucose, high serum triglycerides (TG), and low high-density lipoprotein (HDL) cholesterol levels[4, 14-17].

The precise magnitude of MS in the HIV-infected population is still arguable; but the available data indicate the global prevalence of MS can be regarded as high, ranging from 11.2% up to 45.4% [4, 13], and was also estimated to range from 13% to 58% in Africa[2, 15]. In the sub-Saharan Africa (SSA), the prevalence of MS is not well established [4, 18]. Adults with this problem will have a twofold as likely to die from and are three times as likely to have cardiovascular diseases (CVDs) and a five-fold greater risk of developing type 2 diabetes (T2DM) [2, 7, 11, 14, 19]. In this backdrop and its higher attendant economic and health system consequences of the identification and monitoring of comorbid health risks of HIV and ART [2, 20], MS at present is a global public health issue [2], prominently in the SSA region and Ethiopia, the epicenter of HIV infection [2, 11]. This signifies the importance of knowing what predicts the syndrome.

However, pieces of literature suggested as MS emergence is mostly linked with the interplay of various factors; while several studies revealed the existed direct association of MS with the individual-based factors[4, 14, 21-31]. Inconsistently, some other studies also restated equivocally the explicit effects of all a ranges of the above factors with the incidence of the syndrome [4, 14, 15, 18, 32]. And this implicated the lack of clear evidence about the independent effect of each factor, like individual-based risk factors, HIV/AIDS-related factors, lifestyle or behavioral risk factors, and MS linked risk factors with MS occurrence [22, 33, 34]; which is precipitated with the scarcity primary studies in SSA [24, 30], predominately in Ethiopia[28, 35]; where the majority among the few studies were addressed crosssectional [4, 15, 35, 36], the foundation of this study.

Therefore, this study intended to determine predictors of metabolic syndrome among people living with HIV in the Gedeo-Zone, Southern-Ethiopia, with the employment of unmatched case-control study design, together with the adult treatment panel III criteria as a method to diagnose the subjects with or without the outcome of interest. The findings from this study have significance for public health practice and to establish baseline information for policy and program development. Notably, this study is an extension of the prior large study with multiples of objectives conducted for one year. Hence, for the detail understanding of the methodological procedure employed, you can refer from the article published elsewhere with this citation[37].

2. Methods

2.1. Study design

A health facility-based unmatched case-control study was conducted.

2.2. Setting

This study was conducted in the public health institutions of Gedeo zone, which is 360km, faraway to the south of Addis Ababa (i.e. which is the principal town of Ethiopia), and 86 km to the south of Hawassa city, the main city of the Southern Nations, Nationalities, and Peoples (SNNP) region. It was specifically conducted at randomly selected two hospitals (i.e. Dilla University referral and teaching hospital (DURH) and Yirga-Cheffe primary hospital), and health centers (i.e. Wenago and Dilla town Health centers) chronic HIV care clinics (CHCCs) of the zone, beginning from December 29th, 2017 and January 22nd, 2019 [37]. As per the Gedeo zone ART case team Health management Information system (HMIS) reports, at time of the study, there were a total 3,597 adult PLHIVs (629 ART naïve (370 female, 259 male) and 2968 current on ART (1813 female, 1155 male)). Among these, although (n=537 ART exposed and n=135 ART naïve) were registered in the (CHCCs) of the health centers, but (n=2395 ART exposed and n=412 ART naïve/Unexposed) groups were enrolled and served under the (CHCCs) of the hospitals [37].

As per the current national consolidated guidelines for comprehensive HIV prevention, care and treatment guideline for Ethiopian, all HIV positives are eligible for ART irrespective of their WHO clinical staging and/or CD4 count and the ideal time for ART initiation depends on the clinical condition and readiness of the client, which should be offered on the same day to people who are ready to start. Rapid ART initiation (i.e. defined as the initiation of ART within seven days of HIV diagnosis, provided that there are no contraindications) ought to be offered to all people living with HIV following a confirmed HIV diagnosis, clinical assessment, and assessment of client readiness. As a priority, ART should be initiated in all adolescents and adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with a CD4 count of ≤ 350 cells/mm³. Over all, we have few options of drugs 1st line, 2nd line, and 3rd line regimens. All of those regimens are based on the nucleoside reverse transcriptase inhibitors (NRTI), non nucleoside reverse transcriptase inhibitor (NNRTI) and a boosted Protease Inhibitor (PI). The preferred first-line regimen for adults and adolescents is TDF+3TC+DTG or TDF+3TC+EFV as a once-daily dose. Fixed-dose combinations and once-daily regimens are preferred for antiretroviral therapy [38].

- **Participants**
 - **The source and study population**

The source population of the study was all adults age 18 years and above who were HIV positive and enrolled in the chronic HIV care clinics of the public health facilities (i.e. actively engaged in the delivery

of HIV services), of Gedio zone at time of data collection arranged in the prior survey. A confirmed HIV-positive individual enrolled in the chronic HIV care clinics of the selected health facility chosen to conduct the prior study and identified by then as cases and controls, and fitted the eligibility criteria set for both groups were used as a study population.

- **Case identification procedure**

Cases were identified whenever they came in to those randomly chosen public health institutions' chronic HIV care clinics (CHCCs) (either to take their routine services and or to be enrolled in to it for the first time), and then voluntarily engaged in to the prior study and go through with the physical and the biochemical data collection procedure using the WHO STEPS instrument during the data collection period. The physical measurements data encompassed the body weight, height, waist circumference (WC), and blood pressure data. The biochemical measurements data includes the fasting plasma glucose levels and lipid profiles (Total cholesterol, Triglycerides, High and low density lipoprotein cholesterol) data.

It was accomplished through doing of laboratory tests, arranged in the next day or sometime after completion of the physical measurements of data collection process, but within 8–12 hour overnight fast, by drawing of 3-5 mL Venous blood. Often before analysis, the collected blood samples centrifuged with 5000 (rpm) for 5-10 minutes to separate the serum from the whole blood, and then storing of it to the refrigerator (adjusted at 2-8 °C or -20°C), were performed. Following this, all the biochemical analysis arranged at Dilla University College of medicine and health science hospital clinical Diagnostic laboratory unit was run, using the BS-200E Clinical Chemistry analyzer through applying of a different technique. For instance, the enzymatic colorimetric assay technique was applied for the measurement of Total cholesterol (TC) (CHOD-PAP method) and triglyceride (GPO-PAP method). As well, while the glucose oxidase method (GOD-PAP), and the direct homogeneous enzymatic colorimetric assay methods were employed to measure the glucose, and the remaining the lipid profiles (High density lipoprotein (HDL-c) and Low density lipoprotein (LDL-c)), respectively. The biochemical analysis was made by laboratory technologists, guided with standard operating procedure (SOPs) that explains what to be done from sample collection to result releasing. During analysis, the daily quality control samples together with the individual samples were run before running of the samples, and then the correct functioning of instruments, laboratory reagents, and technical performances were often verified. Lastly, all the physical and biochemical measurements data gathered blindly were used to ascertain and enumerated as a case or as a control, using the below designated case ascertainment method as a base after entry of the data in to the software designated in the analysis section.

- **Methods of case ascertainment**

The cases were ascertained based on the revised National Cholesterol Education Program (NCEP)-Adult Treatment Panel three (ATPIII) criteria[13], by having at least three of the following traits:

1. Waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 35 inches (female) or BMI is >30 kg/m²

2. Dyslipidemia:(Triglyceride ≥ 1.7 mmol/L (150 mg/dl) Or high density lipoprotein cholesterol < 40 mg/dL (male), < 50 mg/dL (female))
3. Blood pressure $\geq 130/85$ mmHg or antihypertensive medication
4. Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dl))) or previously diagnosed with type 2 diabetes mellitus or anti-diabetic treatment.

- **Eligibility criteria for the cases**

Cases were considered in the study if and only if they became a confirmed HIV infected adult's patient, who meet the case ascertainment criteria in the prior study, and then signed the consent form to voluntarily participate in the current study. Cases were excluded if they were refused to participate in the study and they were unable to sign the consent or unable to follow an interview in their native language because of aphasia, reduced consciousness or other reasons such as pregnancy and severe illness.

- **Control selection method**

For each identified cases the corresponding three consecutive controls were likewise randomly determined. They identified from the same sources where the cases were found, after gone through with the whole process that employed to identify the cases. The controls were eligible if they were found within the same age category, but not fulfill exactly the criteria established above to ascertain cases, and or diagnosed with either traits of MS and or has lower than two numbers of MS traits during the prior study time[37]. Controls were excluded if they refuse to participate in the study; we're unable to give informed consent or follow an interview in their native language because of aphasia, reduced consciousness, or other reasons.

The rationale to recruit the case and the control from the same sources (i.e. in the health care institutions) than the community was due to the fact that the PLHIVs can easily be accessed whenever they enrolled and started to take services in the health care institutions; where they represented above the 95% of the PLHIVs in the Gedio zones.

Note that the identification and recruitment of cases and controls procedure was proceed with the assessment of each subject's suitability for the eligibility criteria set for the current study. It was accomplished consecutively whenever they returned back to the clinics for their subsequent routine care, sometime within the study duration. This action was undergone until all the predetermined and identified sample size for the study cases and controls attained.

2.2 Variables

2.2.1 Outcome variable

- i. **Metabolic Syndrome (MS):** diagnosed according to the NCEP-ATPIII criteria[13], as similar as presented in the cases ascertainment method above.

2.2.2 Predictor variables

i. Socioeconomic **and demographic variables:**

- Sex, age, ethnicity, residence, occupation religion, etc .
- **Wealth index:** Household wealth status was estimated by principal component analysis based on ten household variables (such as: the household materials; fuel mainly use for cooking; the place where cooking prepared; the presence of separate kitchen for cooking; main material of the floor of your house; main material of the roof of your house; main material of the exterior wall of your house; number of rooms available in the house for sleeping; the presence of any agricultural land, and the presence of any livestock, herds, other farm animals, or poultry) that measure household assets which is divided into quintiles to represent overall levels of household wealth, such as: quintiles 1-lowest, quintiles 2-second, quantiles3-middle, quintiles 4-fourth, quintiles 5-highest.

ii. HIV/AIDS related variable:

- ART state, duration with HIV and ART, functional status, CD4 levels, WHO staging, and OI's, etc

iii. **Lifestyle/Behavioral risk factors** : All of the following factors were measured according to the Ethiopia steps report on risk factors for non-communicable disease and prevalence of selected NCDs [39]

- **Sedentary:** Minutes spent in sedentary activities on a typical day.
- **Composition of total physical activity:** Percentage of work, transport and recreational activity contributing to total activity.
- **No physical activity by domain:** Percentage of respondents classified as doing no work-, transport- or recreational related physical activity.
- **Domain specific physical activity- mean:** Mean minutes spent in work-, transport- and recreation-related physical activity on average per day.
- **Total physical activity- mean:** Mean minutes of total physical activity on average per day from work, transport and or recreations.
- **Levels of total physical activity according to former recommendations:** Percentage of respondents classified into three categories of total physical activity according to former recommendations.
- **Not meeting WHO recommendations on physical activity for health:** Percentage of respondents not meeting WHO recommendations on physical activity for health (respondents doing less than 150 minutes of moderate -intensity physical activity per week, or equivalent).
- **Former recommendations for comparison purposes:** The three levels of physical activity suggested for classifying populations were low, moderate, and high. The criteria for these levels are shown below.

- **High:** A person reaching any of the following criteria is classified in this category:- Vigorous-intensity activity on at least 3 days achieving a minimum of at least 1,500 MET-minutes/week OR - 7 or more days of any combination of walking, moderate- or vigorous-intensity activities achieving a minimum of at least 3,000 MET-minutes per week.
- **Moderate:** A person not meeting the criteria for the "high" category, but meeting any of the following criteria is classified in this category:- 3 or more days of vigorous-intensity activity of at least 20 minutes per day OR- 5 or more days of moderate-intensity activity or walking of at least 30 minutes per day OR - 5 or more days of any combination of walking, moderate- or vigorous-intensity activities achieving a minimum of at least 600 MET-minutes per week.
- **Low:** A person not meeting any of the above mentioned criteria falls in this category.
- **WHO global recommendations on physical activity for health:** For the calculation of the categorical indicator on the recommended amount of physical activity for health, the total time spent in physical activity during a typical week and the intensity of the physical activity are taken into account. Throughout a week, including activity for work, during transport and leisure time, adults should do at least 150 minutes of moderate-intensity physical activity OR 75 minutes of vigorous-intensity physical activity OR An equivalent combination of moderate- and vigorous-intensity physical activity achieving at least 600 MET-minutes.
- **Metabolic Equivalent (MET):** is the ratio of a person's working metabolic rate relative to the resting metabolic rate. It allows us to calculate total physical activity. One MET is defined as the energy cost of sitting quietly, and is equivalent to a caloric consumption of 1 kcal/kg/hour. Therefore, for the calculation of a person's total physical activity using GPAQ data, the following MET values are used: Work (Moderate MET value = 4.0; Vigorous MET value = 8.0); Transport (Cycling MET value = 4.0 and Walking MET value = 4.0), and Recreation (Moderate MET value = 4.0; Vigorous MET value = 8.0).
- **Physical Activity measurements:** The two most common ways of physical activity (or inactivity): to estimate a population's mean or median physical activity using a continuous indicator such as MET-minutes per week or time spent in physical activity, and to classify certain percentages of a population in specific groups by setting up cut points for a specific amount of physical activity.
- **Alcohol consumption status:** Alcohol consumption status of all respondents (current & past)
 - **Frequency of alcohol consumption:** Frequency of alcohol consumption in the past 12 months among those respondents who drank in the last 12 months.
 - **Drinking occasions in the past 30 days:** Mean number of occasions with at least one drink in the past 30 days among current (past 30 days) drinkers.
 - **Standard drinks per drinking occasion:** Mean number of standard drinks consumed on a drinking occasion among current (past 30 days) drinkers.
- **Smoking Status:** determined based on the number of current and past smokers.
 - **Current Smoking state:** Current smokers among all respondents
 - **Daily smoking:** Percentage of current daily smokers among smokers

- **Initiation and duration of smoking:** Mean age of initiation and mean duration of smoking, in years, among smokers (no total age group for mean duration of smoking as age influences these values).
- **Past Smoking:** number individuals ever smoke any tobacco product in the past
- **Former daily smokers and former smokers:** Percentage of former daily smokers among all respondents and among ever daily smokers, and the mean duration, in years, since former smokers quit smoking

iv. MS related risk factors:

- Are variables measured based on the revised ATP III standard definition. It comprises:
 - **History of Raised Blood Pressure/Diabetes/Cholesterol:** Blood pressure/Diabetes/cholesterol measurement and diagnosis among all respondents.
 - **Blood pressure/ Diabetes/Cholesterol treatment among those diagnosed:** Raised blood pressure/ Diabetes/Cholesterol /treatment results among those previously diagnosed with raised blood pressure/ Diabetes/Cholesterol.
 - **Physical measurements:** elevated waist circumference, body mass index, systolic and diastolic blood pressure.
 - **Biochemical measurements:** elevated fasting plasma glucose, elevated triglycerides, and lower high density lipoproteins.

2.3 Data sources /Measurement

While the sources of data for the outcome variables were individuals physical and biochemical measurements, for the exposure variable were self-reported response from individual interview and the document review. The outcome was measured with the NCEP-ATPIII criteria[13]; which is a standardized techniques employed in the different literatures conducted in the globe, including the study country. The exposure variables were measured as per the standard set in the Ethiopia Steps Report On Risk Factors For NCDs And Prevalence Of Selected NCDs study[39]. This study employed a similar instrument that it gives reliable and valid measures. All the measurement techniques used to ascertain the outcome and exposure variables were comparable for the two study groups (cases and controls).

2.4 Study size

In our previously published article[37] , taking the MS as an outcome, we determined a sample size of 633 participants. Based on the inclusion and exclusion criteria we retrospectively selected 139 cases and 494 controls. This gives 1: 3 cases to control ratio.

2.5 Bias

In order to maintain the internal validity of this study, a validated WHO step instruments and document review data collection checklists were employed to gather quantitative data. The WHO step tool is considered a standardized tool that is freely flexible to investigate NCDs risks of various countries. The use of such a precision tool to collect data on history, physical and biochemical measurements reduces the likelihood of error in methods or interpretation and recording of data. The instruments were translated to the regional language (i.e. Amharic), so that there was easy understanding between the data collectors and the participants and also data collectors obtain data in the same fashion. Additionally, pretesting of the tool was also carried out in adjacent health institutions, not selected for the main study, before the commencement of the data collection process to clarify any ambiguity and to verify the appropriateness of the tools.

Actions against threats of potential biases were addressed accordingly. For example, to eliminate recall bias, we have reduced the period for past events to the last few days. And, cases and controls were interviewed when they came to the health institutions to take their consecutive care arranged after a month of the prior care. To minimize bias related to measurements, the standardized Adult treatment panel three (ATPIII) criteria was used to identify overall metabolic syndrome cases. Controls were also explicitly defined in the method part of this dissertation. To avoid selection bias due to a difference in the number and quality of the service delivered in each health facilities, stratification of these health institutions based on their levels of service delivery and daily patient flow was first made. Although, a consecutive sampling technique was used to randomly select ART exposed and ART naive PLWHs who were receiving their routine care at randomly chosen health centers and Hospital; a total patient flow under each institution for the two comparison groups were first determined, and the required adequate samples from each institution were proportionally drawn.

2.6 Quantitative variable

During data collection, both the case and the controls participants were assessed for their risks using the first step of WHO instrument and the checklist prepared for review of documents. The WHO first step tool gather data on from each individuals on, history of raised blood pressure, diabetes, raised cholesterol and/or CVDs, and lifestyle advice. The checklist consists of questions regarding HIV related factors such as duration diagnosed with HIV, ART status, ART drug types, duration of ART use, CD4+ levels, RNA levels, OI's status and other illness associated risk factors. Later, all data gathered from each individuals cases and control with the same fashion indicated in the above paragraph, were entered into template formed using Epidata (version 3.1) software with the help of two data clerk; eventually validation was performed by using the original data as references. Last of all these, the data were transformed into Statistical Package for Social Sciences (SPSS -Version 22) for analysis.

2.7 Statistical methods

Before application of any statistical methods for the transformed SPSS data, all the necessary data exploration techniques were employed to further cleaning of the data.

Next to this, a range of descriptive data summarization statistical techniques such as proportion, mean, standard deviation was run, and then the results were presented using tables. The dependent outcome variable was dichotomized as having metabolic syndrome (MS) and not having MS. Bivariate logistic regression was performed to examine whether there is a significant association between each independent variable and MS. The following characteristics were considered for inclusion in the models: socio-economic and demographic variables, HIV/AIDS-associated variables, lifestyle-related factors like, and MS-associated clinical risk factors. For each variable, the P-value, and the number and proportion of each variable of case and control were calculated. All variables significant at the ($p < 0.25$) level in the bivariable analysis were included in the initial full model.

Later, a multivariable conditional logistic regression model using a stepwise backward elimination technique was applied to arrive at the final model. In this technique, the analysis started with a full model containing all potential predictor variables collected during the study and these then eliminated in a stepwise fashion using a significance level of 5% ($p < 0.05$). As the socio-economic and demographic factors are conceptually related to the rest factors for the occurrence of MS, the hierarchical model for the analysis is suggested. According to this hierarchical order, we have developed four models. All socio-economic and demographic variables with $p < 0.25$ in the bivariate logistic regression analysis were fitted with model-1. Those variables that were significant in the 1st model ($p < 0.05$) were fitted with model-2. Model-2 contained those significant variables ($P < 0.005$) from model-1 and HIV/AIDS-related variables with $p < 0.25$ in the bivariate logistic regression analysis. As well, model-3 also contained those significant variables ($P < 0.005$) from the 2nd model and lifestyle associated variables with $p < 0.25$ in the bivariate logistic regression analysis. The final model (Model-4) contained those significant variables from model-3 and MS-associated clinical variables. For each model and predictor variables, they're adjusted OR, it's 95% CI and P-value was computed. And, adjusted odds ratio (AOR) with 95% confidence interval and $p\text{-value} < 0.05$ was used as a level of significance accepted in the final models. Before the interpretation of the result, the goodness of fit of the model was checked using the Omnibus test of significance, model summary, Hosmer-Lemeshow goodness of fit test, and the classification table. Multicollinearity and Interaction between all the significant variables in the model were investigated by using VIF, and no correlation between independent variables was seen ($VIF < 10$).

2.8 Ethical clearance

Since this study is an extension of the published article, information about the ethical procedure can be referred from the published article[37].

3. Discussion

To our knowledge, this is one of the few primary studies in the sub-Saharan Africa region, conducted using an integrated system of data collection (WHO stepstools and document review), to examine the predictors of metabolic syndrome among relatively larger number PLHIVs using a strong case-control study design, under one centralized clinical laboratory biochemistry unit.. Whereas, previous studies have

examined the associated risk factors of MS using cross-sectional study approaches among a little number of individuals by employing nonstandard tools. Overall, the study concluded that the age, education, occupation, ART status, WHO-staging, physical activity state, previous history of blood sugar measured, raised BMI, raised WC, elevated fasting blood glucose, elevated triglycerides, and low HDL-cholesterols were found to be an independent predictor of metabolic syndrome. While, education, occupation, ART status, WHO-staging, and physical activity variables were found to be indirect predictors of MS, the rest of the variables were determined as the direct predictors of the syndrome.

It had several limitations, which were emerged from the nature use of a case-control study design, potentially liable for several biases, such as: selection biases, recall bias, information bias and social desirability biases, along with the other problems associated with the current study contexts like the absence of complete matching of it with an important variable (i.e. sex, age, and self-rated wealth), a strict adherence to the ATP III standardized criteria, and the variability's of the studies used for comparison purposes.

As it has been stated above, the odds MS was more likely increased among older age groups than a younger age. Although not consistent on the age groups, but a marked disturbance in the MS with aging has also been reported by several epidemiological studies done worldwide [15, 18, 21, 23, 25, 29, 35, 40, 41]. The observed comparability among the studies might be because, regardless of the difference in the target population, age is a common non-modifiable risk factor that equally likely predisposes all to such health matter. In the reverse, Boshu, et al (2018) [42], Livia D. Akl et al. (2017) [43], Tesfaye DY, et al (2014) [35], and Kaduk et al [44] studies were reported that age is not an independent predictors of MS. The differences across studies might be due to the variation on the studies approaches employed; the differences in the standard criteria used the differences in the target population, along with the time differences. In spite of the observed variances, overall the result might highlighted that succeeding with the advance of ART, the PLHIVs started to have prolonged lifetimes and consequently leads them to be a victim to the identified risk factors; which are likely to inflict an equal impact on PLHIVs as they do in the general population. Notably, this may implicates, with the advance of age of individuals, there will be an inevitable degeneration of organ functions that could potentially imposes a reduction on the quality of the intrinsic physiologic metabolic process, which eventually leads anyone to be at risk of developing either of the risk markers of MS. And hence, looking forward intervention actions aimed at reducing the chronic health problems in general and the syndrome in advance for those PLHIVs aged with the virus will be a vital aspect. Additionally, inconsistent with our finding, while several studies [15, 26, 35, 40, 45-48] noted the direct link of sex with MS incidence, some other studies were also found a similar link of the place of residence with MS [40, 41].

As well, the relation between education and the risk of MS is worth further discussion. The current study result indicated that those PLHIVs with completed secondary schooling education were less likely to develop MS compared to those with no formal education. Correlating with our result, Boshu, et al (2018) [42], Kaduka et al (2012) [44] studies designated that engagement in formal education resulted in 75% increment in the odds of MS (AOR = 0.25, 95% CI [0.072–0.879]). This might confirm that education is a

key to open any locked secrets of life in the world that enable everybody to have a standardized and healthy lifestyle or behaviour, which eventually renders them to be safe from such chronic disease that is highly dependent on individuals habits. Inconsistent with our finding, Livia D. Akl et al. (2017) [43] revealed the absence of a significant association between education and the syndrome.

Notably, our finding also pinpointed that the odds of MS was less likely among un-employed but worked as a home-maker and able to work than those employed in the government institution. Inconsistent with this result, Mashinya et al (2015) [41] study stated that the high unemployment rate was a direct predictor of the syndrome. This unlikeness may be due to the difference in the design used by the former and the later studies. This could be justified due to similar details discussed overhead. As per Mashinya et al (2015) [41] study report, the high unemployment rate might be precipitated with stigma emerged from the viral infection, which may predispose the PLHIVs to high levels of stress; which eventually leads them to develop MS. However, in our view, the observed inverse association may not be out of the domains of differences income earned between the employed and un-employed PLHIVs. This means that, in our country contexts, the unemployed individuals are often earning a lower income that they cannot able to purchase any goods necessary for them to lead a qualified life that it might spontaneously help them to be protected from such high-quality lifestyle-related health problem. Overall, the finding implicated that apart from the actions aimed at design of occupations among HIV infected people might so play an essential part by easing stress-related with unemployment.in indirectly, but still the planning of awareness creation intervention to all, regardless of their employment status may correspondingly play an essential role in the prevention of the risk of acquisition of MS.

Also, our study as well showed that compared with ART naïve a group, the risk of MS was less likely in the ART exposed PLHIVs. It was consistent with several previous studies [26, 35, 40, 49]. Correlating with our finding, G.T. Bune et al. (2019)[37] revealed the existence of higher magnitude of MS among PLWHs participants. As well, Todowede et al. (2019,)[45] meta-study highlighted that the relative risks to estimate for MS among PLHIVs than un-infected population was twofold having with the existed a higher estimated predictive interval for the infected population; this signifies, regardless of the ART status, the risk of acquiring MS among PLHIVs is higher than the general population. This implicates, HIV infection alone is the risk factor that contributed for the incidence of MS. Overall, the finding may accentuate the significances of those traditional risk markers. Nonetheless, still the finding may suggested the significance of further cohort study to be initiated to distinguish the explicit effect of HIV infection and ART exposure on the acquisition of MS in these target population. On the other hand, inconsistent with our finding, quite a lot of studies from developing countries [15, 21, 26, 35, 40, 41, 45, 47, 50] were shown the presence of a direct strong association between ART exposure and MS incidences. With this regards, for instance, G.T. Bune et al. (2019)[37] a comparative crossectional finding revealed that ART has no significant association with the occurrence of MS. This might attribute to the differences in the target population's socio-economic and demographic characteristics, the study approaches, and standard criteria employed by the current and previous studies. And, the implementation of the consolidated guidelines to accelerate the attainment of strategic global and the Ethiopian national HIV goals for 2016–

2021 and the Sustainable Development Goals[38], could be taken as an explanation for the variability's visualized in between the former and the current study.

Furthermore, specific with the ART regimen and in the contrary to our report, a few other studies besides notified the existence of significant differences across ART-regimen [15, 21, 26]. In this respects, still studies have shown inconsistencies' amongst each other about the definite ART regimen there were no consistencies in between. While few studies have agreeable output on the second line regimen, (primarily the protease inhibitors (PI)) as a predictor for the incidence of MS[21, 35, 51], however, few other studies were disclosed that the first-line ART regimen, mainly of the Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) as predictor of MS incidence[15, 26, 35, 42, 51]. In relation to this regimen, studies were further revealed that in patients using Stavudine (d4T)[42, 52, 53] alone, and NRTI as a whole [42, 54] would became risky to acquire dyslipidemia than MS. On the other hands, Tesfaye, D. Y. et al. (2014) [35], Alvarez et al. (2010) [55], Mondey et al.(2007) [56], and Jacobson et al.(2006) [57] studies have shown that this regimen has no association with the incidence of the syndrome. Overall, the finding shown the existence of contradicted knowledge regarding the typical influences of specific ART regimen with the incidence of MS arose from the drug combination given together as one time dose . Also, it might also dictate the direct impact of exposure to any ART regimens on lipid metabolism, endothelial and adipocyte cell function, and mitochondria dysfunction [42, 58], along with the link of the treatment with the incidences of each traits [42, 59] of MS, might be the possible reason for the differences encountered. This implicates to initiates further studies with strong design to differentiate the specific effects each drug regimen with MS incidence.

On top of that, with regards to the HIV/AIDS-related factors, this study was revealed that the odds of MS much times higher in those PLHIVs with more than or equal to three WHO staging, compared with less than three WHO staging. Inconsistent with our finding, van Oosterhout JJ, et al.(2012) reported as it had no association with MS. This may dictate the direct relationship of the WHO staging with the immune reconstruction induced inflammatory process, that could the potential to triggers the release of an inflammatory markers, which are responsible for to facilitate the onset of different intrinsic metabolites, which renders anyone to experience each MS traits first followed by overall MS, could be the possible attribute.

As per the self-reported lifestyle associated factors, although the following factors such as alcohol consumption, smoking habits, 'Khat chewing habits, frequency of consumption of fruit and vegetable, and fat and oil showed no significant association with the presence of MS; however, physical activity was found to be indirect predictors of MS. Studies with this respects are inconsistent with some reporting significant association for smoking habits[41, 50, 60], alcohol consumption [41, 50, 61], and physical activity [41, 62] while others and results of the same study reported no association for 'Khat chewing habits[42], alcohol use[35, 42], physical activity [35, 42, 61], smoking habits [15, 35, 42, 61, 62]. This might be partly explained due to the lower number of individuals grouped under each category that might affect the analysis. Another possible justification the nature of the data relies on self-reporting, which is

liable to response bias. With regards to diet, unrelated to our finding, Jantarapakde, et al (2014) study astonishingly discovered the presence of a direct association between food insecurity (OR 1.8, 95%CI 1.0-3.3, $p = 0.05$)[40]. This could be justified partly due to the time variation, and inconsistent approaches employed by the former and the latter studies.

In the contexts of MS related risks, the current finding notified that raised BMI and WC were directly associated with the incidence of MS. Correlating with our finding, and regardless of the standard criteria employed, several studies were reported similar [45, 61, 63]. For instance, Boshu, et al (2018) [42] study shown that the odds of MS in patients with BMI > 25 kg/m² was 13.4 times higher (AOR = 13.39, 95% CI [3.943–45.525]); as well, Hirgo, et al (2016) likewise pinpointed the presence of significant association with BMI >25 kg/m² ($p = 0.003$) and raised central obesity($p = <0.0001$) with the incidence of MS and criteria. In the reverse, while Tesfaye DY, et al (2014)[35] and Jantarapakde et al (2014) [40] studies were disclosed the presence of an indirect association in between BMI score and MS incidence; whereas Boshu, et al (2018) [42] and Bajaj, et al (2013)[64] studies were revealed the existed indirect relationship in between WC MS. The mismatch may be emerged from the different standard criteria used across studies, the time variation, study approaches, the environmental variations, and the dissimilarity in the socioeconomic, cultural and behavioral characteristics of the target populations.

On top of that, our finding shown that the previous history of blood sugar measured and raised fasting plasma glucose (≥ 110 mg/dl) were variable significantly associated MS occurrence. Correlating with this finding, studies pinpointed that diabetes and or impaired fasting glucose were the most common traits that predict the incidence of MS among PLHIVs [45, 65, 66]. On the other hands, Bajaj, et al (2013) was reported as they had no any significant associated with MS[64]. Moreover, with regards of hypertension and or elevated blood pressure measures, correlating with our study result, even if Bajaj, et al (2013) [64] study disclosed as they don't have association with the incidence of MS, on the other hand several other literatures from developing countries were indicated in the reverse, and prevails that these variables were identified as a common traits and a significant predictor of MS among those PLHIVs[45, 65, 66] [42]. As regards, as Boshu, et al (2018) [42] describes, more of the raised BP measure was the most common feature of abnormalities MS, than impaired fasting plasma glucose commonly seen among PLHIVs. All in all, though our result supported that only diabetes predicts MS, but this doesn't guarantee to conclude that it is the only predictors. Thus, this demands a longitudinal study further to be initiated; so as to understand which of the subcomponent is contributes to the development of MS.

As well, the current study result also shown that elevated triglyceride cholesterol (TGL_c ≥ 150 mg/dl), and lower levels of high density lipoprotein cholesterol (HDL_c <50 mg/dl for female and <40 mg/dl for men) were found to be an independent and a direct predictors of MS. With regards, the finding from Boshu, et al (2018) [42] study done in Jimma Zone, Southwest Ethiopia pinpointed that, lower level of HDL_c than elevated triglycerides as the most common predictor of MS. Inline, Hirgo, A, T et al (2016) [18] study also supported, regardless of the diagnostic criteria, the low HDL_c was the only significantly associated variable with MS ($P<0.005$), primarily in females than males($P<0.005$). Further, in relation with the above contexts, while Jantarapakde et al (2014) [40] study noted that an overall fat redistribution (i.e.

resulted either from “lipoatrophy and or hypertrophy”, which is collectively called as “lipodystrophy”) was a significant predictor of MS (OR 1.8, 95%CI 1.0-3.0, $p = 0.032$), largely in the ART exposed groups ($P < 0.005$). Paradoxically, Boshu, et al (2018) [42], Jantarapakde et al (2014) [40], along with Tesfaye DY, et al (2014)[35] were designated that elevated total cholesterol ($TC > 200\text{mg/dl}$) was the most common direct predictors of all lipid profiles that predicts MS incidence. On the other hand, while Boshu, et al (2018) [42] study shown that low-density lipoprotein cholesterol (LDL_c) was the common lipid profile predicts MS occurrence in those target groups, Bajaj, et al (2013) study was disclosed that none of the above components were significantly associated with the syndrome[64]. The discrepancies observed in between the former and the current studies might be an attribute of the expiations given before, along with the differences observed by the studies on the application of standard diagnostic criteria and the cut of point of each of the biochemical profiles to be decided.

In light of these drawbacks, to increase the generalizability of the findings of this study, a much larger number of sample sizes than required were included in the analysis. The consideration of more than the minimum sample size required has increased the power of the study. On top of that, to see the result of chance, we besides computed the 95% CI as a measure of association between exposure and outcome variables. The confidence interval for most of the variables used in the current study was not wide enough suggesting the adequacy of the sample size. Furthermore, the predictors identified in those health care institutions of the current study can represent HIV- infected people found in the zone. This is because the PLHIVs flows in those health institutions represent the majority of them residing in the Gedio zone. Therefore, the findings of this study can be generalized to the study area and other similar settings in particular.

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4. Conclusion And Recommendations

Generally, the study concluded that while age, previous history of blood sugar measured, raised BMI, WC, IFG, TGL_c, and low HDL_c levels were the direct predictors of MS; education, occupation, ART status, WHO-staging, and physical activity were found to be an indirect predictors of MS. Implicated that the predictors that lead to developing MS components and MS are not yet shown difference with the general populations. It thus, essential to plan routine health education programs to be given to these PLHIVs, in the order to bring behavioral change on modifying their lifestyles. In addition, re-orientate and realizing an integrated care plan that address both the routine care given to PLHIVs and a regular early screening of MS to be underway in the primary health care system, so as to optimize the prevention and management of it, and ultimately to reduce future epidemic cost, in the era of increased population, aging with ART, increased urbanization, and obesity, which have been observed in the SSA region, including Ethiopia. Finally, as a short term intervention the researchers’ needs to evaluate the cost benefits of an integrated

care plan that address both the routine care and the regular MS early screening program, in the meantime to design a longitudinal studies to further investigating the natural course of MS incidences among cohorts of PLHIVs , as a long-time action.

List Of Abbreviations

- **Abbreviations, Numbers and SI Units:** AIDS: Acquired Immunodeficiency syndrome, ART: Antiretroviral Therapy, CVD: Cardio Vascular Disorder, HDL_c: High Density Lipoprotein Cholesterol, IRB: Institutional Review Board, LDL_c: Low Density Lipoprotein Cholesterol, MS: Metabolic Syndrome, NCDs: Non-communicable disease, NCEP/ATP-III: National cholesterol Education program adult treatment panel three, NRTI: Nucleosides reverse transcriptase inhibitors, NNRTI: Non-Nucleosides Reverse Transcriptase Inhibitors, PI: Protease inhibitors, PLWH: People Living with HIV
- **Drug names:** 3TC: Lamuvidine, ABC: Abacavir, AZT/ZDV: Zidovudine, EFV: Efavirenz, LPV/r: Ritonavir boosted/ Lopenavir, NFV: Nelfinavir, NVP: Nevirapine, DDI: Didanosine, ATV/r: Ritonavir boosted/ Atazanavir, and DRV/r: ritonavir-boosted/ Darunavir

Declarations

Ethics approval and consent to participate: All the principles of ethics laid down in the Declaration of Helsinki, and its successive amendments were applied for this study. Hence, ethical clearance was obtained first from Addis Ababa University (AAU) College of Health Sciences school of public health Research and Ethics Committee (REC) (Ref.No.SPH257/09) then from College of health science Institutional Review Board (IRB)(Meeting No.001/2017 and protocol No.0069/16/SPH). Furthermore, the official letter was produced and delivered by the author to the respective Southern Nations Nationalities Regional health bureaus, Gedeo zone and Woreda health bureaus and all of the institutions selected to conduct the study. Data were collected unlinked anonymously, without any personal identifiers. Each individual was enrolled entirely voluntary after written consent was obtained. Any information obtained during the study was retained with the greatest confidentiality. Physical measurement was done by performing measurements at an ART clinic room that has been screened off to maintain the individual's privacy. All biochemical analysis was performed free of charge, and results were provided to the clinicians for further investigation, and possible management[37].

Consent for publication: Not applicable

Availability of data and materials: All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Authors' contributions:

1. **Girma Tenkolu (GT):** Conceptualization study idea, Data collection, analysis, result writing, editing, Investigation, Methodology development, Project administration, Resources allocation, Software application, and Supervision.
2. **Alemayehu Worku (AW):** Conceptualization of study concept, result editing, Investigation, Methodology development, administration, Supervision, journal selection
3. **Abera Kumie (AK):** Conceptualization of concept, result editing, Investigation, Methodology development, Project administration, Supervision, journal selection

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Appendix A. List of table with legends

1. Table1 Proportion and Bivariable association in between the socio-economic and demographic factors and MS
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4. Table 4 Proportion and Bivariable association in between MS related risk factors and MS
5. Table 5 Factors associated with metabolic syndrome in model one, two, three and four

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