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Risk of hypertension in adult patients on antiretroviral therapy: a propensity score matching analysis

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Abstract

Background: Hypertension is a major risk factor that contributes to cardiovascular diseases in adults with HIV infection. Although a relationship exists between antiretroviral therapy (ART) and components of the metabolic syndrome, it is unclear whether HIV or antiretrovirals are explanatory risk factors for hypertension in Persons Living with HIV (PLWH). The present study used propensity-scored-matching (PSM) analysis to estimate ART's average treatment effect (ATT) on blood pressure and hypertension in PLWH.

Objective: The present study used PSM analysis to estimate the average treatment effect of ART on blood pressure and hypertension in patients attending the HIV clinic at the Korle-Bu Teaching Hospital (KBTH) in Accra.

Methods: A hospital-based comparative cross-sectional study was conducted at the HIV Clinic of the Korle-Bu Teaching Hospital in Accra, Ghana. A simple random sampling technique was used to recruit 59 ART-exposed and 59 ART-naïve study participants. The ATT was estimated using the kernel matching or weighting strategy with a bandwidth of 0.06, and standard errors were bootstrapped with 150 replications.

Results: The prevalence of hypertension in the ART-exposed and ART-naive study participants in the final propensity score-matching sample was 42.4% (95% CI, 36.2 - 48.8) and 17.0% (95% CI, 9.3 - 28.9) respectively and the estimated ATT was 26.2% ($p < 0.001$) indicating a statistically significant difference between the ART-exposed group and the ART-naive group. The estimated ATT on systolic blood pressure was 12.0 mmHg (95% CI, 5.7 - 18.3; $p < 0.001$) and that on diastolic blood pressure was 6.1 mmHg (95% CI, 1.3 - 10.8; $p = 0.012$)

Conclusion: A plausible causal link is reported between ART and hypertension. Significant ATT of ART suggests increases in blood pressure values represent a transition from association to causation. This transition could be a significant step in policy formulation in taking preventive action against hypertension and its complications among PLWH.

Keywords: HIV, Hypertension, Propensity score-matching, antiretroviral therapy

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INTRODUCTION

Hypertension is an explanatory risk factor for myocardial infarction, stroke, heart failure, and kidney disease, and it has been established as a major risk factor that contributes to cardiovascular diseases (CVDs) in adults with HIV infection [1, 2]. Hypertension has thus become an important public health challenge, and hypertension, together with CVDs, has been associated with mortality in PLWH [3, 4]. It has been suggested that the degree to which hypertension is related to mortality in HIV-positive patients in sub-Saharan Africa (SSA) has not been specifically addressed [5]. Although a relationship between antiretroviral therapy (ART) and other components of the metabolic syndrome, such as dyslipidaemia and hyperglycaemia, has been established, It is not clear whether HIV or specific antiretrovirals

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(ARVs) are explanatory risk factors for hypertension. Studies have demonstrated an association between HIV infection, ART and hypertension [6-8], but there is no conclusive evidence as other studies have indicated otherwise [9,10]. In this ART era, some studies have raised the possibility that ARVs may induce hypertension [11-14] by accelerating atherogenesis and the subsequent hardening of the blood vessel walls [15]. However, studies on the association between hypertension and ART and the role of different treatment regimens in the pathogenesis of hypertension show conflicting results. Additionally, although a few of these studies have addressed this issue in SSA, these studies also show contradictory results in terms of the association between ARVs and hypertension. Whilst studies in Kenya [16], Ghana [17-20] and South Africa [21] associated hypertension with ART, other studies in Kenya [22], Senegal [23] and South Africa [24] found no association between ART and hypertension. However, in all these conflicting studies on the association between ART and hypertension, the study design and analysis have been done through regression modelling. A systematic review and meta-analysis support an association between ART and increased blood pressure and risk of hypertension in PLWH [25], but there is little evidence of whether this association is causal. In all the studies reviewed [25], the statistical methods employed in examining the association between ART and hypertension have been regression modelling, which is seldom used for causal inferences. However, there is a growing appeal to use statistical methods in observational studies to infer or rule out causal effects, especially in situations where controlled experiments are not feasible due to ethical reasons [26-28]. Inferences which draw on causal effect continue to evolve in modern-day epidemiology, and causal effect has expanded beyond "Hill's Criteria for Causation" [29-31]. One of the statistical methods used in inferring causal effects in observational studies is propensity score matching analysis. Unfortunately, a literature search indicates a dearth of studies in this analysis direction to link ART with increased blood pressure and increased risk of hypertension in PLWH. A study by Nduka et al. [32] using propensity score matching analysis reported a plausible causal average treatment effect of ART on increased blood pressure in PLWH. Propensity score-matching (PSM) analysis is a statistical method of estimating the average treatment effect on an outcome to infer a causal link. Donald B. Rubin first propagated the conceptual foundation of PSM analysis in what is now known as the "Rubin causal model" (RCM) after a series of publications on methods to remove bias and estimate causal effects in observational studies [27, 33-38]. The Rubin causal model is based on the Neyman potential outcomes framework and the idea that depending on a particular treatment assignment, every individual or participant has a potential outcome expressed in counterfactual conditional statements. The model holds that the causal effect of exposure to a treatment, as opposed to being unexposed to that treatment at any given time, is the difference between the outcome measure with and without treatment, assuming no significant difference in the baseline characteristics between the two groups [33, 39]. The present study used PSM analysis to estimate the average treatment effect of ART on blood pressure and hypertension in patients attending the HIV clinic at the Korle-Bu Teaching Hospital (KBTH) in Accra.

MATERIALS AND METHODS

Study design and sites

A hospital-based comparative cross-sectional study was conducted at the HIV Clinic of the KBTH in Accra, Ghana, from February 2016 to May 2016. All consenting HIV–positive patients aged 18 years and above, non-pregnant (female participants) who have attended the HIV clinic for at least six months were eligible for recruitment into the study. Patients excluded from the study were patients with a prior diagnosis of hypertension before HIV infection diagnosis or with sub-optimal adherence to HIV clinic follow-up visits/ART medication or patients on hospitalisation/diagnosed with AIDS.

Sample size and sampling technique

With a 20% attrition rate, a minimum sample size of 49 study participants for each group was calculated based on the estimation of a population parameter for comparative analytical cross-sectional studies [40] using a previously reported prevalence of hypertension in ART-exposed of 28.7% [41] and prevalence of hypertension in ART-naïve of 5.3% [41]. A total of 59 patients were recruited from each group (ART-exposed group and ART-naïve group). A simple random sampling technique was used to recruit potential study participants based on routine clinic attendance. A questionnaire adapted from the WHO STEPwise approach to chronic disease risk-factor surveillance [42] was used for the collection of study participants' data. Data was collected on the socio-demographic characteristics, lifestyle characteristics and family history of cardiovascular disease. Current blood pressure readings were measured and categorised as per WHO, European Society of Hypertension and European Society of Cardiology recommendations [43,44]. Hypertension was defined as current systolic blood pressure (sBP) ≥ 140 mmHg and diastolic blood pressure (dBP) ≥ 90 mmHg on two different days or self-reported medical record history of current antihypertensive therapy [43,44]. BMI was calculated using the Quetelet index [45]. Abdominal obesity (waist-to-hip ratio) was defined as a waist-to-hip ratio of ≥ 0.85 for women and a waist-to-hip ratio of ≥ 0.90 for men [46]. Abdominal obesity (waist circumferences) was defined as > 88 cm for women and waist circumference >102 cm for men [46]. Fasting plasma glucose was classified according to the American Diabetes Association guidelines [18]. The estimated glomerular filtration rate (eGFR) was estimated and classified according to the CKD-EPI creatinine equation [47]. Total cholesterol, HDL-cholesterol, LDL-cholesterol and

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Triglycerides were estimated and classified using the National Cholesterol Education Program, Adult Treatment Panel III (NCEP/ATP III) guidelines [48]. HIV and ART-related data were extracted from the clinical folders of the study participants. ART exposure was categorised into ART-exposed and ART-naïve. ART-exposed was defined as the administration of either two NRTIs (or one NRTI and one NtRTI) + one NNRTI or 2 NRTIs (or one NRTI and one NtRTI) + one PI. ART-naïve were patients yet to initiate ART (as at the time of the study). Stata® 14 software was used to analyse the data.

Data analysis

Variables used in estimating ATT of ART on hypertension were current hypertension status (outcome variable) and ART exposure (treatment variable). The covariates used were age, sex, religion, employment status, marital status, educational level, family history of hypertension/CVD, smoking status, alcohol intake, baseline BMI, physical activity, fruit intake, HIV infection duration, HIV-type, baseline sBP, baseline dBP, baseline CD4 T-cell count, administration of antihypertensive medication and presence of co-morbidity. A logistic regression was used (with ART exposure as the outcome variable and covariates/confounders as exploratory variables) to estimate a propensity score for each study participant. The balance of the estimated propensity scores across the treatment group (ART-exposed) and the comparison group (ART-naive) for common support was checked visually by a box plot and objectively by Student's t-test. The balance of covariates across the treatment group and the comparison group was checked using a standardised difference of not more than 10%. This iterative process was repeated several times (deleting, re-categorisation and inclusion of interaction terms of covariates) until the estimated propensity scores were balanced across treatment and comparison groups and the entered covariates balanced across treatment and comparison groups within blocks of the estimated propensity scores. The average treatment effect on the treated was estimated using the kernel matching or weighting strategy with a bandwidth of 0.06. Standard errors were bootstrapped with 150 replications. The balance of covariates after the kernel weighting strategy was checked by comparing the standardised differences before and after matching and weighting (achieving < 10% standardised difference), evaluation of the ratio of variances (between 0.5 and 2.0), and graphically using a dot graph. Post-estimation analysis for the extent of influence of unobserved covariates (sensitivity test) was done using Rosenbaum bounds (the rbounds syntax in Stata®).

RESULTS

Characteristics of ART-exposed and ART-naive study participants

A total of 18 covariates (covariates either hypothesised to be associated with both ART exposure and hypertension

Table 1. Characteristics of study participants in propensity score-matching analysis

Characteristics	ART-exposed N = 59	ART-naive N = 59	p-value
Age (years), mean ± SD	45.6 ± 9.7	43.8 ± 8.7	0.147
Sex, n (%)			
Female	45 (76.3)	44 (74.6)	0.830
Male	14 (23.7)	15 (25.4)	
Education, n (%)			
None	8 (13.6)	9 (15.2)	0.129
Basic	33 (55.9)	24 (40.7)	
Secondary	16 (27.1)	25 (42.4)	
Tertiary	2 (3.4)	1 (1.7)	
Religion			
Christianity	53 (89.8)	51 (86.4)	0.569
Moslem	6 (10.2)	8 (13.6)	
Employment, n (%)			
Unemployed	6 (10.2)	7 (11.9)	0.769
Employed	53 (89.8)	52 (88.1)	
Marital status, n (%)			
Single	11 (18.6)	10 (16.9)	0.394
Married/Co-habiting	24 (40.7)	30 (50.9)	
Divorced/Separated/ Widowed	24 (40.7)	19 (32.2)	
Smoking status, n (%)			
Never smoker	57 (96.6)	56 (94.9)	0.648
Ever smoker	2 (3.4)	3 (5.1)	
Alcohol status, n (%)			
Abstainer	41 (69.5)	38 (64.4)	0.557
Drinker	18 (30.5)	21 (35.6)	
Family history of CVD, n (%)			
No	51 (86.4)	53 (89.8)	0.569
Yes	8 (13.6)	6 (10.2)	
Exercise, n (%)			
Never/Rare	40 (67.8)	41 (69.5)	0.843
Most times	19 (32.2)	18 (30.5)	
Fruit intake, n (%)			
Never/Rare	18 (30.5)	20 (33.9)	0.694
Most times	41 (69.5)	39 (66.1)	
BMI category, n (%)			
< 25.0 kg/m^2	30 (50.8)	28 (47.5)	0.713
≥ 25.0 kg/m^2	29 (49.1)	31 (52.5)	
HIV-type			
HIV-I	43 (72.9)	44 (74.6)	0.937
HIV-II	1 (1.7)	1 (1.7)	
Mixed (HIV-I and HIV-II)	15 (25.4)	14 (23.7)	
Duration of HIV infection (years), mean ± SD	7.8 ± 3.7	7.2 ± 3.7	0.271
Baseline CD4 T-cell count, n (%)			
≤ 350 cells/µL	37 (62.7)	26 (44.1)	0.042
> 350 cells/µL	22 (37.3)	33 (55.9)	
Baseline sBP, mean ± SD (mmHg)	113.6±17.6	116.1±7.0	0.322
Baseline dBP, mean ± SD (mmHg)	69.3±11.5	71.5±1.8	0.199
Antihypertensive treatment, n (%)			
No	48 (81.4)	49 (83.1)	0.810
Yes	11 (18.6)	10 (16.9)	

BMI=Body mass index; CVD=Cardiovascular disease; N=Total number of study participants; n=Number of respondents per characteristic; SD=Standard deviation

or hypothesised to be associated with hypertension, excluding covariates which are affected by ART exposure and treatment) were examined for inclusion in estimating the propensity scores (Table 1). Table 1 analysis indicates that only baseline CD4 T-cell count was significantly different (at α=0.05) between the ART-exposed group and the ART-naive group, suggesting its potential as a confounder to the effect of ART and thus needed to be adjusted.

Estimation of propensity scores for ART-exposed and ART-naive study participants

A logistic regression model was used to estimate the propensity score for each study participant with the covariates: age, sex, education, marital status, employment, smoking status, alcohol drinking status, family history of CVD, fruit intake, exercising, baseline BMI category, HIV type, baseline systolic blood pressure, baseline diastolic blood pressure, antihypertensive medication and baseline CD4 T-cell count. The mean ± standard deviation of the estimated propensity scores was 0.81 ± 0.08, and the median was 0.82 (IQR, 0.76 - 0.87). Although this may indicate skewness of the estimated propensity scores, the skewness value of -0.80 is within the range of -1.0 to 1.0 and is thus considered good to demonstrate a normal distribution [32]. The results also indicate that the estimated propensity scores were grouped into five optimal blocks. The "common support" for ART-exposed ranged from 0.5599 to 0.9616 with a mean of 0.8186, and for ART-naive ranged from 0.5128 to 0.9182 with a mean of 0.7748. A box plot, a k-density plot and a histogram of the estimated propensity scores indicating the region of "common support" are shown in Figures 4, 5 and 6, respectively. Visual analysis of the box plot (Figure 4) indicates a wide area (over 70%) of estimated propensity scores overlap between the ART-exposed and the ART-naive study participants, as depicted by their median points. Figure 5 further collaborates this observation as the shapes of the normal distribution of the estimated propensity scores for ART-exposed and ART-naive were similar.

Table 2. Covariates balance indicators in the propensity score-matching study participants

Covariate	ART-exposed Means	ART-naive	p-value	% bias	Variance ratio
Age (years)	44.95	45.37	0.613	-4.5	1.05
Sex	0.24	0.23	0.794	2.4	-
Religion	1.11	1.09	0.408	7.1	0.81
Education	2.22	2.28	0.342	-8.6	0.95
Marital status	1.94	1.96	0.786	-2.5	1.00
Employment status	1.12	1.11	0.706	3.4	1.09
Smoking	0.04	0.04	0.741	2.8	-
Alcohol	0.31	0.31	0.977	0.3	-
Family history of CVD	0.11	0.12	0.847	-1.8	-
Fruit intake	1.33	1.31	0.654	4.1	1.03
Exercising	1.71	1.68	0.483	6.4	0.95
Baseline BMI category	1.51	1.51	0.971	-0.3	1.00
HIV type	1.52	1.58	0.426	-7.5	0.94
Duration of HIV infection (years)	7.54	7.80	0.544	-7.0	0.92
Baseline sBP (mmHg)	114.57	114.66	0.953	-6.1	1.03
Baseline dBP (mmHg)	70.03	70.75	0.503	-6.1	0.92
On anti-hypertensive treatment	0.17	0.16	0.825	2.0	-
Baseline CD4 T-cell count category	1.58	1.55	0.494	6.3	0.98

BMI = Body mass index; CVD = Cardiovascular disease; dBP = diastolic blood pressure; sBP = systolic blood pressure

Table 3. Estimated average treatment effect of ART exposure on hypertension and blood pressure values

Outcome	Estimated ATT [95% CI]	p-value	Gamma (Γ) 95% CI	Hodges-Lehmann
Hypertension, %	26.2 [13.3-39.1]	<0.001	1.6	2.1
Systolic blood pressure (mmHg)	12.0 [5.7-18.3]	<0.001	2.5	3.4
Diastolic blood pressure (mmHg)	6.1 [1.3-10.8]	0.012	1.9	2.4

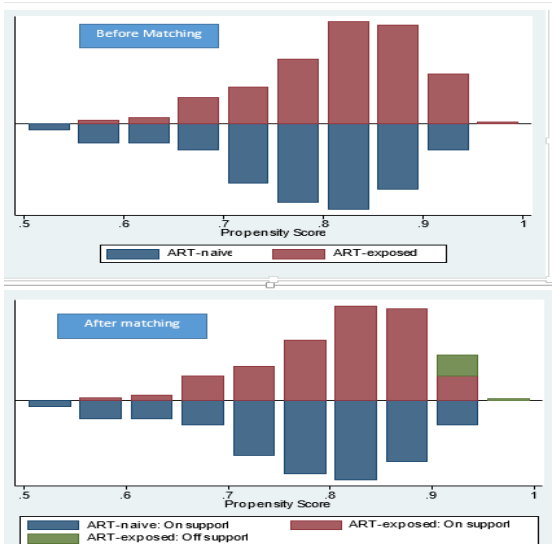

Figure 1. Distribution of estimated propensity scores before and after matching

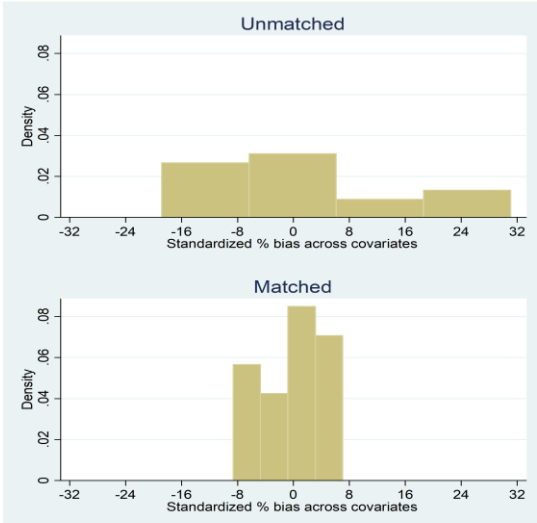

Figure 2. Histogram showing standardized percentage bias before and after propensity score matching

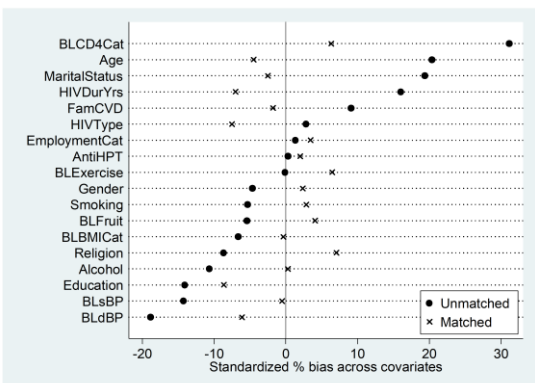

Figure 3. Standardised % bias across each covariate before and after matching

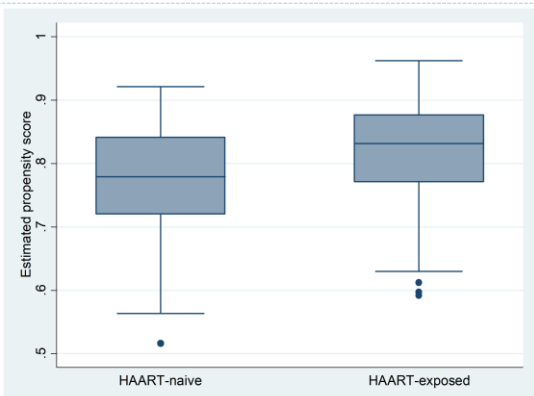

Figure 4. Box-plot of estimated propensity score among ART-exposed and ART-naive study participants before matching

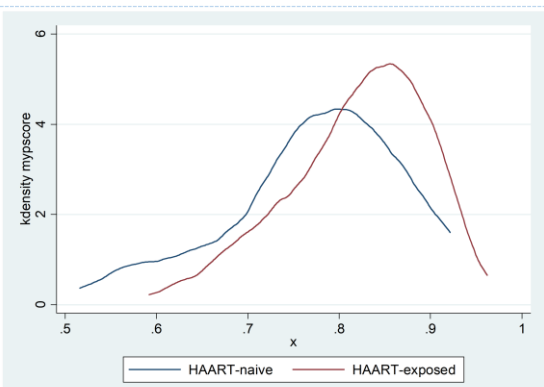

Figure 5. K-density plot of estimated propensity scores among ART-exposed and ART-naive study participants before matching

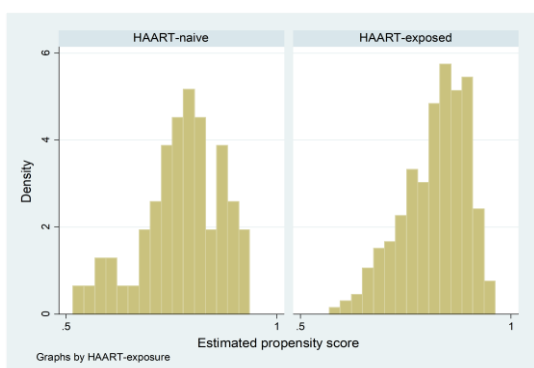

Figure 6. Histogram of estimated propensity score among ART-exposed and ART-naive study participants before matching

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Figure 6 confirms the visual inspection of the distribution of the normally distributed propensity scores and further indicates a high likelihood of achieving a region of common support. In addition, the test of balancing property of the estimated propensity scores for each covariate was balanced for all 18 covariates.

Matching of ART-exposed to ART-naive study participants using the estimated propensity scores

The kernel weighting strategy was used to match the ART-exposed group to the ART-naive group with a common bandwidth of 0.06. There were 118 study participants (59 ART-exposed individuals and 59 ART-naive individuals) before matching. Matching on the kernel weight yielded 114 study participants comprised of 55 ART-exposed individuals and 59 ART-naive individuals (final model). Table 2 shows the variance ratios of the unmatched and matched data. The mean and the median standardised bias reduced from 10.5% and 8.9%, respectively, in the unmatched data to 4.1% and 3.8% in the matched data. The individual variance ratio in the matched data ranged from 0.92 to 1.22. The total variance ratio of the matched data was 1.72, indicating the acceptability of the matching procedure. Figure 1 shows the distribution of estimated propensity scores before and after matching, indicating a good matching between the ART-exposed and ART-naive study participants with minimal loss of individuals due to lack of "common support". Figure 5 shows the standardised percentage bias across all covariates before and after matching. Visual inspection shows a reduction in bias after matching, as seen by a decrease in percentage bias spread from about -20 to 30 in the unmatched data to about -8 to 8 in the matched data (Figure 2). Figure 3 shows the standardised percentage bias for each covariate before and after matching, indicating a successful matching of the ART-exposed to the ART-naive study participants. Analysis of Figure 3 indicates a reduction in standardised percentage bias for 14 included covariates after matching.

Estimation of ATT of ART exposure on hypertension and blood pressure values

The prevalence of hypertension in the ART-exposed and ART-naive study participants in the final propensity score-matching sample was 42.4% (95% CI, 36.2 - 48.8) and 17.0% (95% CI, 9.3 - 28.9), respectively. The estimated ATT was 26.2% ($p < 0.001$), indicating a statistically significant difference between the ART-exposed group and the ART-naive group (Table 3). Thus, ART-exposed patients were 26.2% more likely to be hypertensive than ART-naive patients. Post-estimation analysis indicated a gamma level of 1.6 at a 95% confidence interval. The estimated average treatment effect of ART exposure on hypertension is sensitive to an unobservable covariate, increasing the odds of ART exposure by 60% (Table 3). In addition, at a gamma (Γ) level of 2.1, the Hodges-Lehmann point estimates encompass zero, indicating that a high increase in the likelihood of being an ART-exposed individual due to an unobservable characteristic, which also increases being hypertensive is required to explain the observed level of estimated average treatment effect (Table 3). The estimated ATT on systolic blood pressure was 12.0 mmHg (95% CI, 5.7 - 18.3; $p < 0.001$), indicating a significant difference in systolic blood pressure between the ART-exposed group and the ART-naive group (Table 3). Similarly, the estimated ATT on diastolic blood pressure was 6.1 mmHg (95% CI, 1.3 - 10.8; $p = 0.012$), indicating a statistically significant difference in diastolic blood pressure between the ART-exposed group and the ART-naive group (Table 3). Post-estimation sensitivity analyses indicate a gamma level of 2.5 and 1.9 at a 95% confidence interval for systolic and diastolic blood pressure, respectively (Table 3). Gamma levels for Hodges-Lehmann point estimates were 3.4 for systolic blood pressure and 2.4 for diastolic blood pressure (Table 3), indicating results of the estimated treatment effect of ART exposure on systolic and diastolic blood pressures were insensitive to selection on unobservable covariates, i.e. unlikely that such confounding variables would not have been observed.

DISCUSSION

The study demonstrated that using PSM analysis, the estimated average treatment effect of ART increases the prevalence of hypertension and also increases both systolic and diastolic blood pressure values. This study comes at a time when the association between ART and hypertension is ridden with conflicting results, although there are several postulations on the pathophysiology of ART's effect on hypertension and CVD in general. The unfortunate dearth of literature on the causal average treatment effect of ART on hypertension, as observed by Nduka et al. [25], makes it difficult to compare the present results with previous studies. However, this study is the second in line in this analysis direction. A study published by Nduka et al. [32] reported an estimated causal average treatment effect (ATT) of 7.85 mmHg and 7.45 mmHg increases in systolic and diastolic blood pressure values. The results of the present study indicate an estimated average treatment effect on the treated (ATT) of 12.0 mmHg on systolic blood pressure and 6.1 mmHg on diastolic blood pressure. Although the ATT on diastolic blood pressure is comparable to the ATT reported by Nduka et al. [32], the ATT on systolic blood pressure is higher than the previous study. However, considering the fact that a 20 mmHg point is needed to move a non-hypertensive individual maximum threshold systolic blood pressure from 120 mmHg (non-hypertensive) to 140 mmHg (hypertensive) whilst a 10 mmHg is needed for diastolic blood pressure (from 80 mmHg to 90 mmHg), the present study's ATT on both systolic blood pressure and diastolic blood pressure is plausible. The present study also reported an estimated ATT of 26.2% points on hypertension, which is coherent with conclusions from several studies suggesting a plausible causal relationship between ART and hypertension and related blood pressure levels in PLWH. Reports from the MACS indicated a

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temporal relationship between ART and increased blood pressure levels [49]. A systematic review with meta-analysis involving 39 studies (of varied study designs and settings) indicated an epidemiological association between ART and increased systolic and diastolic blood pressure levels and increased risk of hypertension in PLWH [25].

The interest in using PSM analysis to infer or otherwise a plausible causal effect of treatment, i.e. cause-effect relationships, especially in situations where RCT is not practicable due to logistical constraints or ethical reasons, is growing [26-28]. This is consistent with the modifying concept of causation in epidemiology, which has expanded and gone beyond the simple relationships established by "Hill's Criteria of Causation" [29-31] to the use of statistical methods in testing causal hypotheses [26-28]. To the best of our knowledge, this study is the second to use propensity score-matching analysis to examine a plausible causal relationship between ART and blood pressure values in PLWH; the first is the study reported by Nduka et al. [32]. The role played by ART in elevating blood pressure values and consequently increasing the risk of hypertension in PLWH has been attributed to a myriad of interacting pathophysiological pathways, including ART-induced vascular and endothelial dysfunction [49-51], an exaggerated immune response following initiation of ART [52], chronic inflammation and adipose and liver dysfunction [51]. Worth noting is that although experimental animal data is lacking on the reversal or preventive effect of ART on blood pressure [32], a published clinical trial demonstrated a significant reduction in blood pressure when patients were switched from a first-generation non-nucleoside reverse transcriptase inhibiter (nevirapine) to a second generation non-nucleoside reverse transcriptase inhibiter (rilpivirine) [53]. It has been suggested that the use of nevirapine in ART combination is consistent with the rise in the prevalence of hypertension and associated cardiovascular disease mortality rates seen since the onset of the ART era [3,32,49,54].

Limitations

Some variables used in the PSM analysis were extracted from the clinical folders of study participants, and hence, their appropriateness depends on the extent of correctness attached to these data when they were collected. Blood pressure readings were performed at two different clinic days and may be subject to fluctuation secondary to human and equipment-related factors; however, this was adjusted in the analysis, and any measurement difference would likely be of a non-differential type. Another limitation of this study is that data were based on measurements taken at one point according to clinical indications and will be assumed to reflect their chronic condition. Study participants did not receive a definitive diagnosis of hypertension based on the measurements done, but nonetheless, the 2012 WHO STEPwise approach to chronic disease risk-factor surveillance instrument [42] was used, which is a standardised tool for chronic disease risk-factor surveillance.

Study strengths and contribution to knowledge

To the best of our knowledge, this is the first study to associate a plausible causal relationship between ART and the increased prevalence of hypertension using propensity score matching analysis. In addition, this study is the second, to the best of our knowledge, to infer a plausible causal relationship between ART and increased systolic and diastolic blood pressure values using propensity score matching analysis. Another strength of this study is the use of a statistical model (propensity score-matching analysis) to investigate a potential causal link between ART and blood pressure; otherwise, ethical challenges would have hindered the design of a randomised control trial to investigate the potential causal link. The inference of causal link using estimated ATT reflects a higher level of evidence and a substantially lower risk of not accounting for residual confounding compared with other observational studies which used regression modelling [27,55]. Another strength of the study is the methods used in ensuring that the selected covariates in the propensity score-matching sample were sufficiently and appropriately balanced between the ART-naive group and the ART-exposed group using a comprehensive three-step process; differences in means or proportions, standardised bias after matching and ratio of variances [27]. The covariates selected in the estimation of the propensity score included the risk factors of hypertension known to persist in the general population.

Conclusion

Due to the ongoing debate on the association between ART and hypertension, a propensity score matching analysis was employed to examine the average treatment effect of ART on hypertension and blood pressure values. The present finding acknowledges ART-associated increase in blood pressure as an entity, and results of the PSM analysis indicate a plausible causal relationship between ART and hypertension with increases in both systolic and diastolic blood pressure. The reported plausible causal link between ART and hypertension/increases in blood pressure values, which represents a transition from association to causation, could be a significant step in policy formulation in taking preventive action against hypertension and its complications among PLWH.

DECLARATIONS

Ethical considerations

The Ethical and Protocol Review Committee of the College of Health Sciences, University of Ghana, gave the ethical study clearance [Protocol Identification Number: MS-Et/M.3-P 4.4/2015-2016]. Permission was obtained from the clinician-in-charge of the Fevers Unit at the KBTH, and informed consent was sought

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and obtained from each study participant. Patients' data were de-identified during data capture, entry, analysis and storage by ensuring only the study codes were used consistently throughout the project cycle.

Consent to publish
All authors agreed to the content of the final paper.

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Competing Interest
The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions
ETN and RAT conceived and designed the study. RMA, FA and BS gave conceptual advice. RMA and RAT assisted in funding acquisition. ETN, RAT, RMA and BS did the statistical analysis and drafted the manuscript. RMA, RAT, FA and BS reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data
The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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