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Diabetes Mellitus as a risk factor for stroke among Nigerians: A systematic review and meta-analysis

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ABSTRACT

Background: Diabetes mellitus is one of the modifiable risk factors for stroke. Stroke is common in Nigeria, but there is a paucity of national data on the frequency of diabetes in stroke. This study aimed to estimate to what extent diabetes a risk factor for stroke in Nigeria.
Methods: The study design is a systematic review, and the PRISMA guidelines were strictly followed. African Journal Online (AJOL), PubMed, SCOPUS and Google Scholar were systematically searched. The Newcastle-Ottawa scale was used to assess the quality, heterogeneity was determined with the I^2 statistic, and the DerSimonian Laird random effect model was selected for the meta-analysis.
Results: The studies were distributed across different regions of the country. The total sample size was 9397. The weighted average age of the patients with stroke was 53.7 years. The attributable risk of diabetes in stroke, among Nigerian patients, was 0.20 (95% CI: 0.17–0.22; $p < 0.0001$). The attributable risk has been rising steadily since the advent of the new century, and it is relatively higher in southern Nigeria.
Conclusion: The attributable risk of diabetes in stroke, among Nigerian patients is high. This varies across the regions but it is rising progressively nationally.

1. Introduction

Cardiovascular diseases are the most common cause of mortality worldwide. [1] In 2019, the World Health Organization (WHO) estimated that 18.6 million people died from cardiovascular disease. [2] This accounted for 33% of global mortalities. It is of great concern that 3 out of every 4 deaths from cardiovascular disease occur in middle- and low-income countries, which are already overburdened by the impact of communicable diseases. [3] Stroke accounts for 1 out of 6 cardiovascular deaths. [4] The modifiable risk factors for cardiovascular disease include hypertension, diabetes, smoking, dyslipidaemia, sedentary lifestyle, unhealthy diet, excessive alcohol intake, and obesity. Table 1 below shows the hazard ratio of various cardiovascular risk factors for cardiovascular disease. [5] It shows that the impact of cardiovascular risk factors varies with income level. In Nigeria, the incidence of cardiovascular disease has been rising partly due to the growing prevalence of cardiovascular risk factors, urbanization, and the adoption of the western lifestyle. [6] Diabetes mellitus is a major cardiovascular risk factor in Nigeria. [7–9]

Diabetes mellitus is a chronic metabolic disorder characterized by chronic hyperglycemia caused by a defect in insulin secretion and/or action. Globally, over 400 million people have diabetes, which is estimated to directly cause over a million deaths annually. [10] Fig. 1 shows that the projected prevalence of diabetes will continue to escalate virtually across all the regions of the world. Diabetes mellitus, when poorly controlled, can accelerate atherosclerosis, thereby predisposing people to cardiovascular morbidity and mortality. [11] Diabetes mellitus is associated with macrovascular complications such as stroke, coronary artery disease, and peripheral artery disease.

Nigeria has the largest number of people living with diabetes in sub-Saharan Africa. [12] In a meta-analysis, the prevalence of diabetes in Nigeria was estimated at 5.8%. [13] The documented risk factors for diabetes in Nigeria include a family history of diabetes, urbanization, adoption of the western lifestyle, obesity, sedentary lifestyle, smoking, and advancing age. [13] Some of these factors have been on the rise due to varied reasons, which implies a growing prevalence of diabetes in Nigeria. [14] Unfortunately, the challenges of managing diabetes in Nigeria are becoming increasingly daunting despite the escalating

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Table 1
Modifiable risk factors for cardiovascular disease and mortality across different countries of varying income.

	Risk factor	Hazard ratio		
		HIC	MIC	LIC
1	Hypertension	1.5	2.1	1.9
2	Diabetes mellitus	2.3	1.6	2.1
3	Smoking	2.6	1.7	1.3
4	Dyslipidaemia	1.6	1.3	1.4
5	Physical inactivity	1.4	1.2	1.3
6	Obesity	1.1	1.3	1.3

HIC – high-income countries, MIC- middle-income countries, LIC- low-income countries.

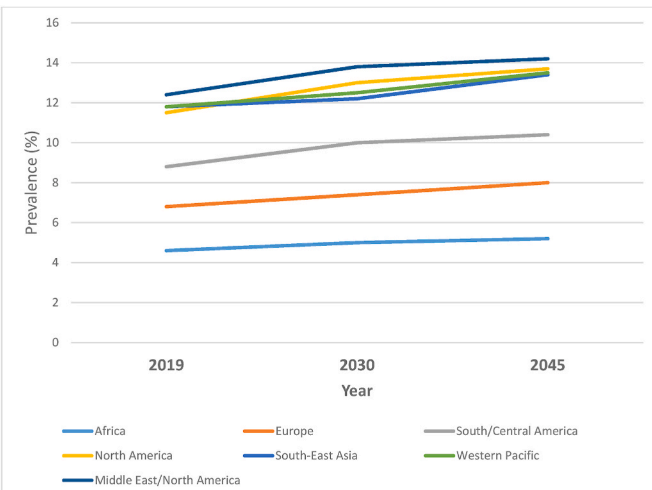

Fig. 1. Projected rising prevalence of diabetes globally.

prevalence of the disease in the country. [15] Awareness and advocacy for diabetes are inadequate in Nigeria. [16]

The clinical value of this study is to examine the degree to which diabetes contributes to stroke in Nigeria to justify the need for intensified efforts at preventing diabetes and stroke. Similarly, it is known that cardiovascular risk factors vary among the regions in the country, and this study would show if and how diabetes affects the frequency of stroke across the regions.

Stroke is an acute neurological syndrome characterized by a sudden shortage of blood supply to the brain, spinal cord, or retina. [17] Table 2 shows the common causes of death globally, according to the WHO. [18] It shows that stroke is the second commonest cause of death globally. Similarly, stroke is the second leading cause of disability among adults who are over 50 globally. [19] Unfortunately, despite the inadequacy of resources, low and middle-income countries account for 70% and 87% of death and disability respectively attributed to stroke globally. [19] As depicted in Fig. 2, stroke can be classified into ischaemic stroke and haemorrhagic stroke. Ischaemic stroke results from the blockage of the

Table 2
Causes of death worldwide.

Causes of death	Frequency (%)
Ischaemic heart disease	16.0
Stroke	11.0
Lower respiratory tract infection	5.0
Neonatal conditions	4.0
Dementias	3.5
Diarrhoeal diseases	3.1
Diabetes mellitus	3.0
Kidney diseases	2.8

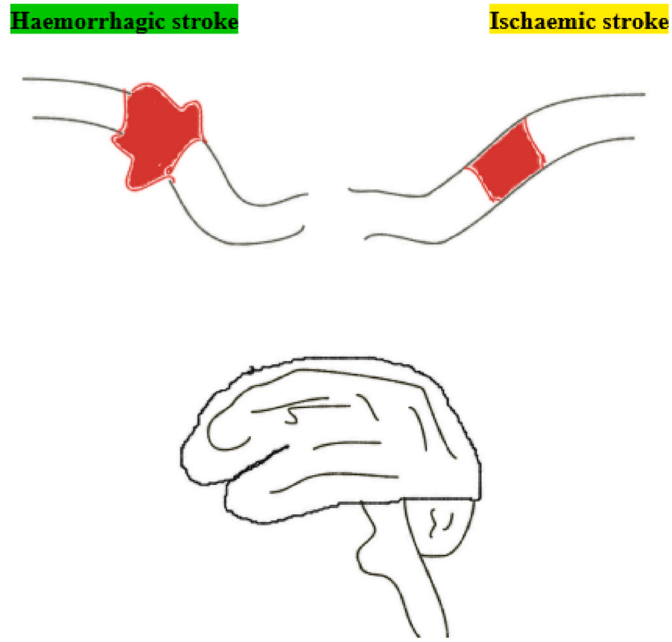

Fig. 2. Classification of stroke-ischaemic and haemorrhagic.

vessels by a local thrombus or an embolus, while haemorrhagic stroke essentially occurs when the artery ruptures. Ischaemia-reperfusion injury elicits a pathologic cascade leading to apoptosis of neurons, and this has been highlighted as a major mechanism of brain injury during stroke. [20] Molecularly, there is enhanced expression of p53 which is associated with augmented activities of the caspase-induced apoptotic cascade. Additionally, some protective genes are downregulated during reperfusion injury. Fig. 3 shows the modifiable and non-modifiable risk factors for stroke.

Nigeria is the most populous black nation in the world, and the point prevalence of stroke in the country is 56–1331 per 100 000 population although this varies from rural areas to urban areas. [21,22] Case fatality is reported to be as high as 40%. [23] The main risk factors for stroke in Nigeria are similar to those in other countries but certain conditions that are not among the top risk factors in developed nations, such as sickle cell disease and HIV/AIDS, are also prominent in Nigeria. [24] In a multicentric case-control study across Nigeria and Ghana, the

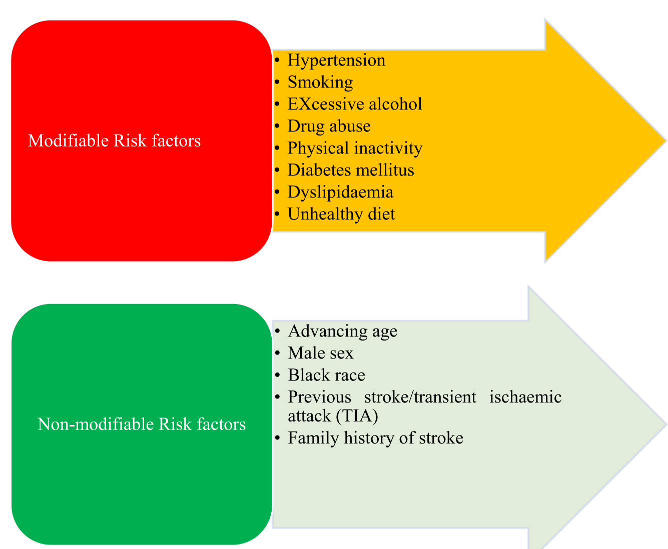

Fig. 3. Categorization of the risk factors for stroke.

identified risk factors for stroke are shown in Fig. 4. [25]

Diabetes mellitus is an established risk factor for cardiovascular diseases such as myocardial infarction and stroke, but the magnitude of the risk varies across different parts of the world. [26] There are scanty studies in sub-Saharan Africa on the extent of the risk diabetes mellitus constitutes to stroke. This study aims to estimate to the degree diabetes a risk factor for stroke in Nigeria.

2. Methods

The study design is a systematic review and meta-analysis. The search for relevant articles was per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study's PRISMA diagram is shown in Fig. 5. The relevant medical databases searched were African Journal Online (AJOL), PubMed, SCOPUS and Google Scholar. Preprint databases (Research Square, SciELO and medRxiv) were equally searched. The grey literature was also explored. The search was limited to studies published on or after January 1, 2000 in Nigeria. Table 3 shows the list of the search items. Boolean operators 'AND', 'OR' as well as 'NOT' were utilized to optimize the search results.

Retrieved studies were analyzed independently by the authors. Only studies that reported the actual or deduced attributable risk were selected. The final selection was determined by the simple majority of the authors based on the selection criteria. Data on the location, study design, sample size, mean age of the population, and attributable risk of diabetes were extracted. Attributable risk is defined as the portion of the disease rate attributable to the exposure factor in an epidemiological context. [27] The data were organized with the Microsoft Excel spreadsheet (Redmond, Washington, United States).

For the quality assessment of the selected studies, the Newcastle-Ottawa scale was used. Using the Agency for Healthcare Research and Quality (AHRQ) standards, 72% of the studies were good, 23% were adequate, and 5% were poor. [28]

The DerSimonian Laird random effect model was utilized for the meta-analysis. The heterogeneity of the selected studies was determined using I^2 statistic and the Cochran's Q test. I^2 values of 25%, 50%, and 75%, correspond to small, moderate, and large amounts of heterogeneity respectively. [29] Q statistic value greater than 75–100 was considered substantial heterogeneity. [30] The risk of publication bias was determined by the symmetry of the Begg's funnel plot. All the analyses were performed with Meta XL version 5.3 (EpiGear International Ltd., Northwestern University, Sunrise Beach, Queensland, Australia.). Meta XL is an add-in software for Microsoft Excel specifically designed for meta-analysis.

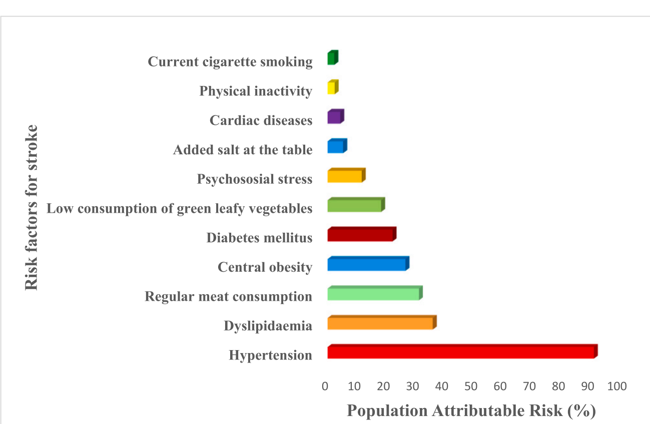

Fig. 4. How different risk factors contribute to the occurrence of stroke in Nigeria and Ghana.

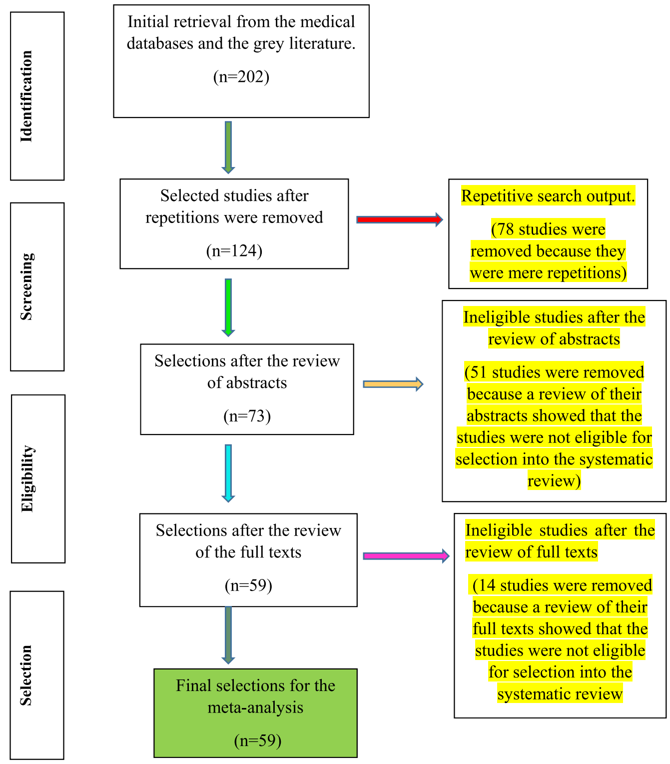

Figure 5: The PRISMA flow diagram.

Fig. 5. The PRISMA flow diagram.

Table 3
Search items.

S/No	Search item
1.	Diabetes/diabetes mellitus
2.	Stroke
3.	Risk/risk factors
4.	Attributable risk
5.	Nigeria/Nigerians
6.	Epidemiology
7.	Acute stroke
8.	Ischaemic stroke
9.	Haemorrhagic stroke

3. Results

As shown in Fig. 5, fifty-nine studies met the selection criteria for the study. The geographic distribution of the study is shown in Table 4. The studies were distributed across the different regions but more studies were done in the South-West. The characteristics of the studies are shown in Table 5. As shown in Fig. 6,all the studies are observational but a significant proportion (about 40%) of the studies were prospective in design.

Table 4
Geographical distribution of selected studies.

	Region	Number of studies
1	South-West	18
2	North-West	10
3	North-Central	7
4	Federal Capital Territory	7
5	North-East	6
6	South-East	5
7	South-South-	6
	Total	59

Table 5
Characteristics of the study.

S/No	Study	Year	Design	Sample size	Age (years)	Attributable Risk
1	Nnachi [31]	2003	CR	65	60.4	0.22
2	Amu et al. [32]	2005	CC	80	60.6	0.26
3	Kolapo et al. [33]	2006	P	96	54.0	0.26
4	Komolafe et al. [34]	2006	R	283	–	0.09
5	Karaye et al. [35]	2007	CR	81	55.8	0.11
6	Komolafe et al. [36]	2007	P	135	62.0	0.16
7	Wahab et al. [37]	2007	P	100	58.6	0.23
8	Atta [38]	2008	P	80	59.1	0.30
9	Oni et al. [39]	2008	R	28	62.2	0.11
10	Onwuchekwa et al. [40]	2009	R	54	–	0.11
11	Abubaka et al. [41]	2010	R	260	55.7	0.09
12	Desalu et al. [42]	2011	R	101	68.0	0.24
13	Obiako et al. [43]	2011	P	66	–	0.14
14	Musa et al. [44]	2012	P	91	56.2	0.05
15	Owolabi & Ibrahim [45]	2012	P	71	31.9	0.04
16	Owolabi & Nagoda [46]	2012	P	273	55	0.17
17	Ukoha et al. [47]	2012	R	37	–	0.24
18	Watila et al. [48]	2012	P	524	56.4	0.10
19	Abubakar et al. [49]	2013	P	75	57.7	0.11
20	Abubakar & Sabir [50]	2013	R	260	55.7	0.08
21	Alkali et al. [51]	2013	P	272	56.4	0.24
22	Ekeh et al. [52]	2013	P	120	55	0.32
23	Eze et al. [53]	2013	R	108	61.6	0.39
24	Bwala [54]	2014	P	272	56.4	0.24
25	Ogbera et al. [55]	2014	CR	137	62.2	0.24
26	Okokhere et al.	2014	R	99	66.2	0.17
27	Adefemi [56]	2015	CC	101	64.1	0.22
28	Ademiluyi [57]	2015	P	100	62.5	0.29
29	Watila et al. [58]	2015	CC	65	47.2	0.18
30	Ekeh et al. [24]	2015	P	120	55	0.37
31	Olatunji et al. [59]	2015	R	88	69.7	0.14
32	Omojowolo [60]	2015	P	101	51	0.13
33	Oyinloye et al. [61]	2015	R	69	37.8	0.24
34	Philip-Ephraim et al. [62]	2015	R	50	60.8	0.06
35	Sanya et al. [21]	2015	CR	18	58.2	0.12
36	Alkali et al. [63]	2016	CR	344	55.8	0.26
37	Ezennaka [64]	2016	CR	100	57.7	0.4
38	Igetei [65]	2016	P	100	61.5	0.28
39	Okoronkwo [66]	2016	P	122	54.5	0.16
40	Olamoyegun et al. [67]	2016	R	103	56.2	0.16
41	Owolabi et al. [68]	2016	P	536	56.1	0.16
42	Yau et al. [69]	2016	CC	100	56.4	0.23
43	Jaiyeola et al. [70]	2017	R	283	45.2	0.05
44	Ojo & Onyegiri [71]	2017	R	60	59.4	0.18
45	Ogunjimi [72]	2017	CC	80	57.6	0.25
46	Olaleye & Lawal [73]	2017	R	783	59.9	0.23
47	Olasheni et al. [74]	2017	R	143	61.5	0.27
48	Onwuegbuzie & Reng [75]	2018	R	120	59.9	0.55
49	Ekenze et al. [76]	2019	CR	17	60.1	0.04
50	Eze et al. [77]	2019	P	152	40.7	0.21
51	Kolade-Yunusa et al. [78]	2020	R	148	54	0.28
52	Arabambi et al. [79]	2021	CR	230	59.9	0.09
53	Dahiru et al. [80]	2021	P	111	57.5	0.19
54	Fayemiwo et al. [81]	2021	CC	100	57	0.28
55	Ibrahim et al. [82]	2021	R	276	67.3	0.2
56	Nwoha et al. [83]	2021	CR	149	63.4	0.27
57	Onwuegbuzie et al. [84]	2021	CC	113	–	0.34
58	Osaigbovo et al. [85]	2021	P	246	59.5	0.19
59	Sulaiman et al. [86]	2021	P	501	53.9	0.13

CC- Case-control.
CR- Cross-sectional.
P- Prospective.
R-Retrospective.
- Not available.

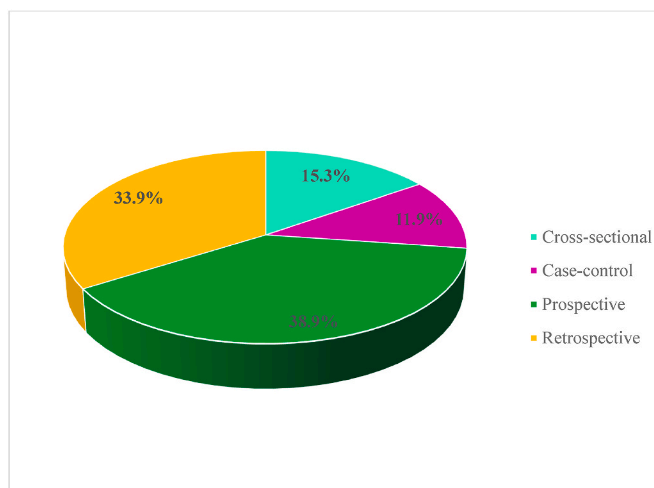

Fig. 6. Types of study designs.

The total sample size was 9397. The weighted average age of the patients with stroke was 53.7 years. The forest plot is shown in Fig. 7. The attributable risk of diabetes in stroke, among Nigerian patients, was 0.20 (95% Confidence Interval: 0.17–0.22; $p < 0.0001$). I^2 was 88%, which suggests large heterogeneity. This is corroborated by the Q statistic value of 409. The funnel plot is shown in Fig. 8. The symmetry of the funnel suggests some publication bias. Fig. 9 shows that the attributable risk of diabetes in stroke has been steadily rising since the advent of the new century. The regional variation in the attributable risk is represented in Fig. 10. The attributable risk is lower in the core north (North-West and North-East) compared with the south.

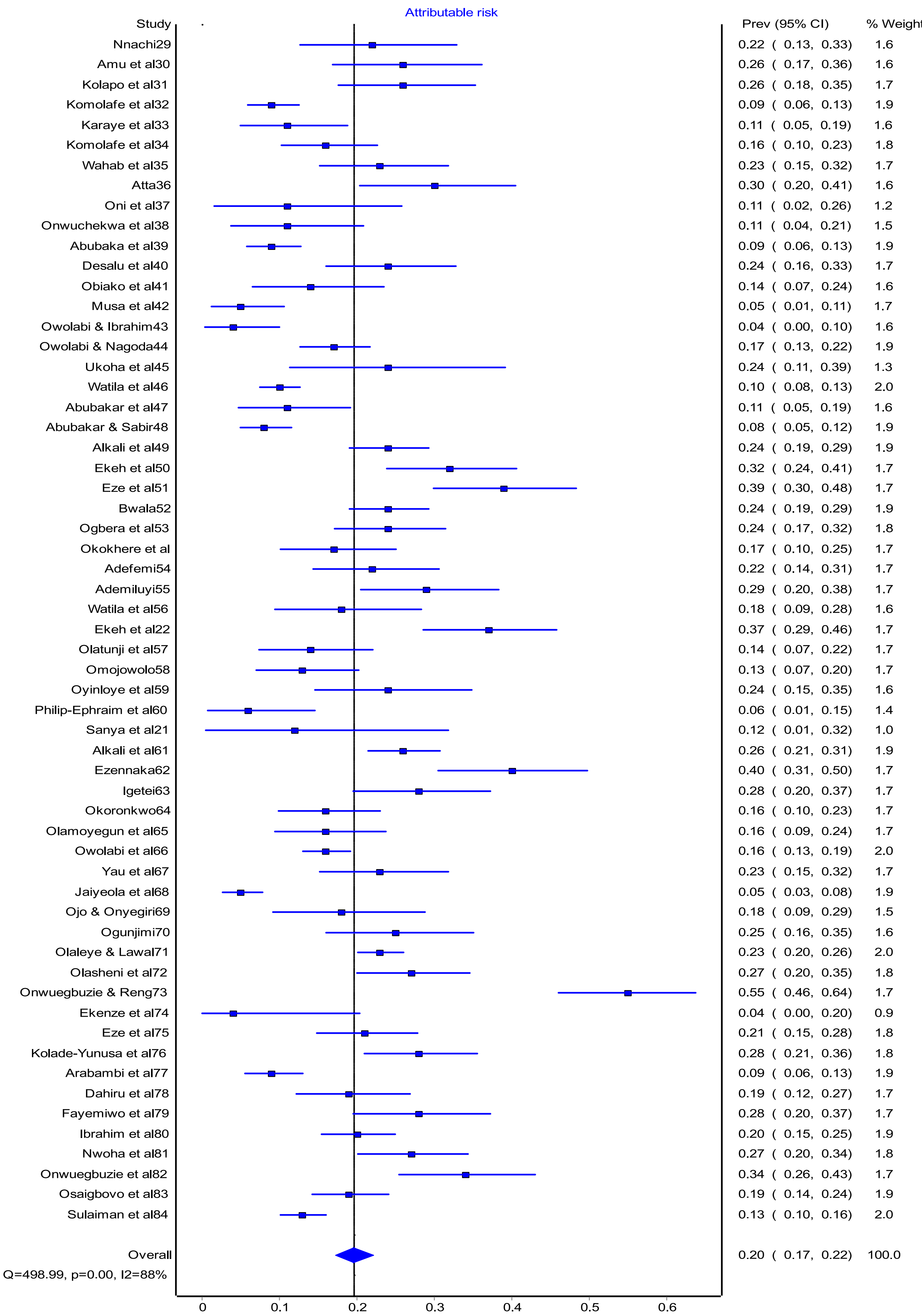

Fig. 7. Forest plot.

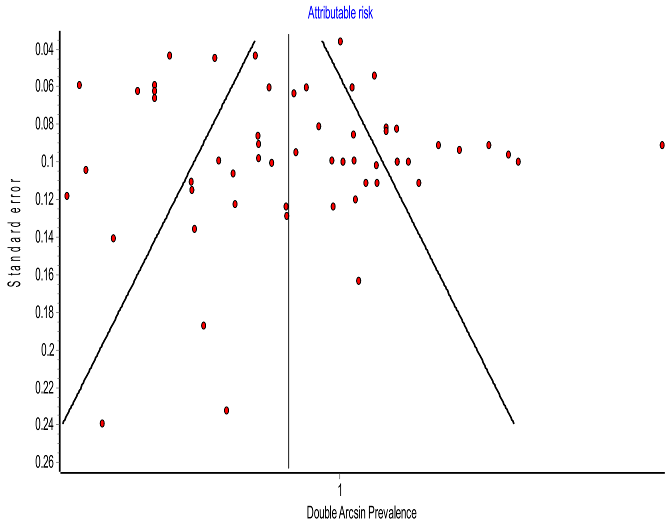

Fig. 8. Funnel plot.

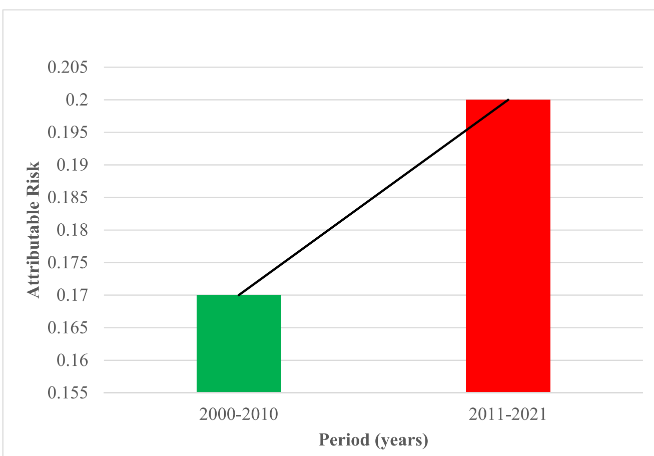

Fig. 9. Trend of the attributable risk.

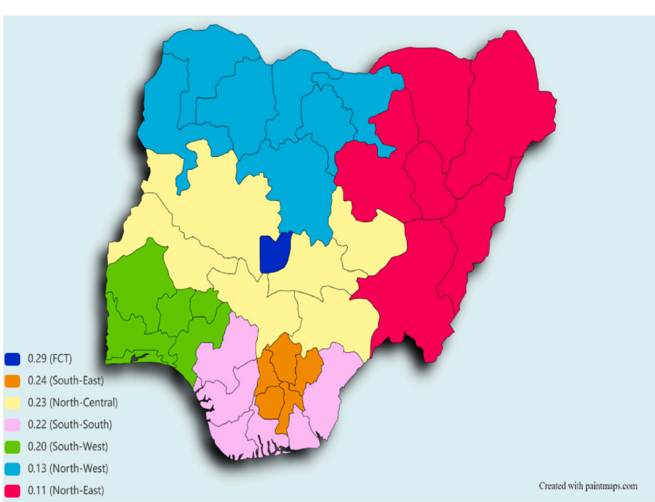

Fig. 10. Regional variation in the attributable risk.

4. Discussion

Fifty-nine studies met the eligibility criteria and were employed for the analysis. In a developing nation where studies are much less conducted, compared with the developed world, the number of studies utilized for the meta-analysis, with a sample size of almost 10 000 individuals, is significant enough to give a representative conclusion. Flather et al. have suggested that larger meta-analyses (with several hundreds of sample sizes) tend to provide more reliable results. [87] There is a paucity of systematic reviews with meta-analyses on the risk factors for stroke in Africa but the few ones previously conducted employed 12–27 studies with a sample size ranging between 2000 and 6000 individuals. [88–90] This further affirms the notion that the number of studies and the sample size of the present study are representative enough.

In Nigeria, as found in the present study, the population attributable risk of diabetes mellitus in stroke patients is 0.20 (95% CI: 0.17–0.22; p < 0.0001). This implies that about 20% of Nigerians who develop stroke equally have diabetes mellitus. This is comparable with other sub-Saharan countries where attributable risks of 0.11–0.38 have been reported. [91–95] The prevalence of diabetes has been rising in Nigeria and it is an established cause of atherosclerosis which could lead to stroke. [13,26] Diabetes mellitus has also been associated with worse outcomes in individuals that have had stroke. [96] Similarly, risk factors such as obesity, hypertension, dyslipidemia and smoking are predictors of both diabetes and stroke which can also account for the high frequency of diabetes among Nigerians who have had stroke. [97,98]

Pathophysiologic processes such as endothelial dysfunction, arterial wall thickening and stiffness, systemic inflammation, oxidative stress, dysregulated coagulation and widespread microangiopathy are some of the proposed mechanisms linking diabetes with stroke. [26,99] Nitric oxide-mediated vasodilation is impaired in people with poorly controlled diabetes which affects smooth muscle contractility culminating in vascular dysfunction. [100] Inflammatory markers such as C-reactive protein, interleukin-1, interleukin-6 and tumor necrosis factor-alpha which are elevated in patients with diabetes have equally been reported to be raised in patients with stroke too. [101,102] In addition, lifestyle modifications such as achieving and maintaining a healthy weight, exercise, smoking cessation, avoiding excess alcohol ingestion and intake of fruits and vegetables have been shown to reduce the incidence of both stroke and diabetes, still suggesting a strong link between them. [103]

Interestingly, the present study has also demonstrated a steady rise in the frequency of diabetes among Nigerians with stroke at the turn of the 21st century. In Nigeria, the prevalence of diabetes has been steadily increasing over the years due to the growing adoption of western diets, sedentary lifestyle, urbanization and improving life expectancy (as more people are not dying from communicable diseases). [13] This could partly explain upstroke in the frequency of diabetes among stroke patients. Studies on the burden of stroke are now better designed and powered enough to capture the frequency of the risk factors for the disease. [104] While the awareness of hypertension, which is the most significant risk factor for stroke in Nigeria, is increasing, this cannot be said about the awareness of diabetes among the Nigerian populace. [105,106]

This study also shows a dichotomy in the regional frequency of diabetes in stroke among Nigerians. The core North (North-East and North-West) are associated with a lower attributable risk (0.11–0.13) compared with the South (South-East, South-South and South-West) which is 0.20–0.24. This is striking partly because Uloko et al. in their meta-analysis on the regional prevalence of diabetes in Nigeria, also documented a lower prevalence of diabetes in Northern Nigeria (3.0–5.9%) compared with Southern Nigeria (4.6–9.8%). [13] Adegboye et al. reported that the Northern Nigerians (consisting mostly of Hausa and Fulani ethnic groups) tend to eat whole-grain based diet with less red meat unlike the Southern Nigeria where refined and calorie-dense diet is much more prevalent, according to Olatona & Obrutu. [107,108] This could probably contribute to the lower prevalence of diabetes in Northern Nigeria and its lower attributable risk to stroke. In addition, hypertension, which is a risk factor for diabetes (and stroke) is also more common among adults in Southern Nigeria (42.1–52.8%) when compared with those in Northern Nigeria (20.9–27.5%). Genetic tendencies, apart from established environmental factors, are also possible contributors to this dichotomous phenomenon but more studies are needed to confirm this plausible hypothesis. However, it must be stated that the number of studies was quite limited and not uniformly distributed thereby making regional head-to-head comparison somewhat questionable. This is a limitation of the study.

The strength of the current study is that it is the first to utilize a systematic review coupled with meta-analysis to estimate the attributable risk of diabetes to stroke in Nigeria. The sample size is huge and the studies are widely distributed across the geopolitical regions. It has also reiterated an interesting dichotomy in the distribution of cardiovascular risk factors across Northern and Southern Nigeria which could stimulate further research in pinpointing the reasons behind this observation.

A limitation of the study is that all the studies are observational and causality cannot be readily established. Other confounders which might influence the attributable risk of stroke are also outside the scope of the current study.

5. Conclusion

The attributable risk of diabetes in stroke, among Nigerian patients, is high. This however varies across the regions, being higher in Southern Nigeria, compared with Northern Nigeria. Also, across all regions, the frequency of diabetes among individuals who have had stroke is rising steadily.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Available of data and materials

Available on request.

Competing interest

None.

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Authors' contributions

TAA contributed to the conception, data collation, writing and editing of the manuscript. IMD contributed to the writing and editing of the manuscript. AIM contributed to the writing and editing of the manuscript.

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