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Ethnic and region-specific genetic risk variants of stroke and its comorbid conditions can define the variations in the burden of stroke and its phenotypic traits

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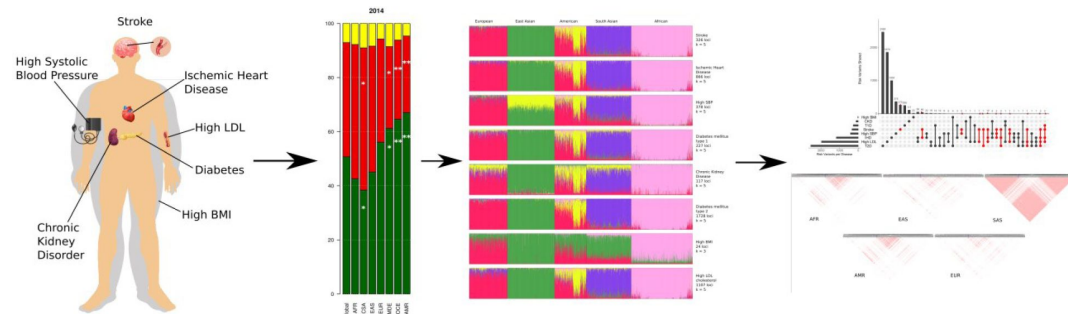
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Abstract

Burden of stroke differs by region, which could be attributed to differences in comorbid conditions and ethnicity. Genomewide variation acts as a proxy marker for ethnicity, and comorbid conditions. We present an integrated approach to understand this variation by considering prevalence and mortality rates of stroke and its comorbid risk for 204 countries from 2009 to 2019, and GWAS risk variant for all these conditions. Global and regional trend analysis of rates using linear regression, correlation and proportion analysis, signify ethnogeographic differences. Interestingly, the comorbid conditions that act as risk drivers for stroke differed by regions, with more of metabolic risk in America and Europe, in contrast to high SBP in Asian and African regions. GWAS risk loci of stroke and its comorbid conditions indicate distinct population stratification for each of these conditions, signifying for population specific risk. Unique and shared genetic risk variants for stroke, and its comorbid and followed up with ethnic specific variation can help in determining regional risk drivers for stroke. Unique ethnic specific risk variants and their distinct patterns of Linkage Disequilibrium further uncover the drivers for phenotypic variation. Therefore, identifying population and comorbidity specific risk variants might help in defining the threshold for risk, and aid in developing population specific prevention strategies for stroke.

Graphical Abstract



eLife assessment

This paper provides a **useful** analysis of the variation of the burden of strokes across geographic regions, finding differences in the relationship between strokes and their comorbidities. This dataset and the correlations found within will be a resource for directing the focus of future investigations. The statistical analyses are **incomplete**.

Introduction

Stroke affects over 101 million people worldwide and is ranked the second most fatal disease in the world, with 6.5 million deaths in 2019¹. Comorbid conditions of stroke are critical contributors to burden of stroke and the duration of the comorbid conditions can further determine the severity of stroke risk or mortality. Prevalence for comorbid conditions range from 43% to 94% and estimates can go as high as 99% above 66 years of age². Prevalence and mortality risk in stroke has often been evaluated from socio-economic viewpoint, but it is also critical to understand the differences in drivers such as comorbid conditions. It is the accumulated risk of comorbid conditions that enhances the risk of stroke further. Are these comorbid conditions differentially impacted by socio-economic factors and ethnogeographic factors. This was clearly evident in COVID era, when COVID-19 differentially impacted the risk of stroke, possibly due to its differential influence on the comorbidities of stroke.

Mortality in Stroke, its subtypes and their comorbid conditions have a strong ethnic bias^{3,4,5}. Genetics act as surrogate marker for ethnogeographic indices. It is important to understand which comorbid conditions are influenced by socio-economic indices, and how they impact the risk of stroke and their underlying genetic basis. A Danish study reported the effect sizes of association with comorbid conditions for stroke to have 15% higher mortality risk in presence of diabetes mellitus with end-organ damage, 20% for peripheral vascular disease, 25% for chronic pulmonary disease, 35% for congestive heart failure and atrial flutter, 45% for moderate to severe renal disease, and 1.8- to 2.4-fold for mild to severe liver disease⁶. A UK Biobank study on stroke multimorbidity reported 1.5x higher risk of mortality in those with 2 additional comorbidities and a $\approx 2.5\times$ higher risk of mortality in those with ≥ 5 comorbidities over seven years⁷. Thus, the differential impact of comorbid or multimorbid conditions contributing to the additive effect of illness burden needs to be addressed from an ethnogenetic perspective. Devising an appropriate strategy for prevention of stroke burden, needs a careful evaluation of the underlying genetic signature for each of these comorbid conditions and distinguishing their ethnic bias.

The objective of the study was to understand what determines the differences in stroke burden around the globe. Variations in burden of stroke could be influenced by comorbid conditions, and incidentally both stroke and its comorbid conditions can be influenced by ethnogeographic factors and genetics can act as a stable proxy marker for all. To resolve this, we considered the prevalence and mortality of a total of eleven disease conditions, comprising of stroke and its comorbid conditions, across different continents and ethnicities from 2009 to 2019. The disease conditions were further stratified as per their ethnogeographic locations and their genetic risk variants extrapolated from GWAS data. This study would provide insights on the regional patterns of the burden of stroke and its comorbid conditions, and help in resolving it from an ethnic and genetic viewpoint. These insights would further aid in developing and strategizing regional and ethnic specific needs for prevention of the risk of comorbid conditions and stroke.

Results

Global mortality, incidence and prevalence rates of stroke and its comorbid conditions

Globally, stroke ranks as the second most fatal disease in 2019 (84.2/100000, 95%UI 76.8-90.2) among the eight diseases analyzed, preceded by ischemic heart disease (IHD; 117.9/100000, 95%UI 107.8-125.9) as shown in figure S1 and table S1. High systolic blood pressure (high SBP) ranks as the most fatal comorbid disease condition with an age-standardized mortality rates (ASMR) of 138.9/100000 [95%UI 121.3-155.7] among all conditions. Within stroke subtypes, ischemic stroke (IS) ranks highest globally with ASMR of 43.5/100000 [95%UI 39.08-46.8], followed by intracerebral hemorrhage (ICH) at 36.0/100000 [95%UI 32.9-38.7] and subarachnoid hemorrhage (SAH) at 4.7/100000 [95%UI 4.1-5.2]. The ranking of the ASMRs of the diseases follow the same trend throughout the last decade with minor exceptions, where high body-mass index (high BMI) improved its rank in 2014 by swapping with high low-density lipoprotein cholesterol (high LDL), and type 1 diabetes (T1D) dethroned chronic kidney disease (CKD) in 2019.

Global trends in crude and age-standardized incidence rates (ASIRs) show that stroke incidence ranks fourth, while IHD is on top followed by T2D and CKD (fig.S1, table S1). Crude incidence rates of stroke and its subtypes increases in the last decade but ASIRs decreases, with exception of IS where an increase in ASIR was observed. Among other diseases, IHD, type 2 diabetes (T2D) and T1D show a continuous increase in the last decade, with T2D (280.1/100000, 95%UI 258.8-303.9) surpassing IHD (274.0/100000, 95%UI 242.9-306.4) in 2019 in crude rates.

The global trend between crude and age-standardized prevalence rates (ASPRs) revealed that the ranking of stroke remains at sixth position throughout the years (fig.S1, table S1). Among stroke subtypes, IS ranks higher over the ICH and SAH. The comorbid conditions, high SBP and high BMI, ranks first and second followed by CKD and T2D, and interestingly all rank above stroke. We also observe that though there is a continuous increase in prevalence rates in the last decade, the ranking of stroke or its comorbid conditions does not change over the years, with the exception of T1D ASPRs overtaking ICH. We were keen to understand if these global trends of ASMR and ASPR are influenced by region and ethnicity.

Ethno-regional differences in mortality and prevalence of stroke and its major comorbid conditions

We observed interesting patterns of ASMRs of stroke, its subtypes and its major comorbidities across different regions over the years as shown in **figure 1a** [↗](#), S3, **table 1** [↗](#) and S2. When assessed in terms of ranks, high SBP is the most fatal condition followed by IHD in all regions, except Oceania (OCE) where IHD and high SBP swap ranks. Africa (AFR; 206.2/100000, 95%UI 177.4-234.2) and Middle East (MDE; 198.6/100000, 95%UI 162.8-234.4) have the highest ASMR for

high SBP, even though they rank as only the third and sixth most populous continents (fig. S2), respectively. Both high SBP (-0.64% to -2.25% EAPC) and IHD (-0.45% to -1.17% EAPC) show a decreasing trend for ASMRs in all regions. However, only Europe shows a significant decrease for high SBP (-2.26%; $P=0.009$) and IHD (-2.37%; $P=0.006$) in the decade. Stroke has a decreasing trend for ASMRs with East Asia (EAS) and Europe showing a significant decrease of -2.2% ($P=0.021$) and -2.6% ($P=0.03$), respectively. Stroke has the highest mortality in EAS (127.1/100000, 95%UI 104.9-150.5 in 2019), and is the only region that ranks stroke higher than IHD. Though EUR, MDE and Central & South Asia (CSA) have ASMRs similar to global rates for stroke, CSA ranks stroke as the third most fatal factor, while America (AMR), Europe and MDE ranks it fifth. Oceania (62.1/100000, 95%UI 34.1-90.2) and America (40.3/100000, 95%UI 36.2-43.1) have lowest rates for stroke in 2019.

Among the stroke subtypes, ICH and IS show maximum ethnogenetic differences in mortality rates (14.1/100000 to 61.4/100000) and ranking (4th to 9th) in 2019. While ICH shows a significant decrease in ASMR in EAS (-3.53%, $P=0.009$), IS shows a significant decrease in Europe (-2.37%, $P=0.06$). High BMI and high LDL rank in top five but their mortality rates differed across all regions, with the highest rates for both in MDE. Only Europe shows a significant decrease in high LDL (-2.53%, $P=0.03$) over the decade. MDE has the highest ASMRs due to IHD and high SBP, followed by AFR, CSA, EAS and EUR, all having rates higher than global. All continents have similar mortality rates for T2D and CKD across the years, except Oceania, where the T2D rate is nearly three times CKD rate. Africa has the highest mortality rate for T1D (1.59/100000, 95%UI 1.2-1.9).

ASPRs also showed an interesting pattern of distribution, and, in contrast to mortality, show an increase over the decade (fig. 1b and S4, table 2 and S3). Highest ASPRs were observed for high SBP across all regions, except America, MDE and Oceania, where high BMI has most prevalence. While EAPC of high SBP showed significant decrease in all regions (-0.38% to -1.77%), except CSA, high BMI showed a significant increase (1.77% to 5.6%) in all (table 2). The ASPR ranking of CKD and T2D rose to top five, in sharp contrast to their ASMR rankings. Prevalence of CKD (EAPC 0.24% to 0.7%) and T2D (EAPC 0.6% to 2.18%) is significantly increasing in all regions. For all other diseases, the pattern of ranking and rates across regions were stable with minor exceptions. Stroke ranks sixth for ASPRs in all regions, and it is interesting to note that ASPRs of all the comorbid conditions, except T1D, rank above stroke. While Europe shows a significant decline in ASPRs of stroke (-0.9%, $P=0.008$) and IS (-0.85%, $P=0.03$) across the years, EAS shows a significant increase for stroke (0.7%, $P=0.02$) and IS (1.09%, $P<0.001$). Globally, T1D swapped its ASPR ranking with ICH in 2014, largely influenced by the significant increase in ASPRs in MDE (2.83%, $P<0.001$). However, the highest prevalence of T1D is in Europe and Oceania. The prevalence of IHD has remained nearly constant in all continents in the last decade, except Oceania (-0.43%), America (-0.49%) and MDE (-0.27%) which shows a significant decrease. In 2019, MDE has the highest prevalence for IHD (4843.02/100000, 95%UI 4243.02-5442.58), while America (1695.6/100000, 95%UI 1530.8-1871.9) has the lowest ASPR, less than half the rate of the MDE. Globally, T1D swapped its ASPR ranking with ICH in 2014, largely influenced by the significant increase in ASPRs of T1D in MDE (2.8%, $P<0.001$). However, the highest prevalence of T1D is in Europe and Oceania. We were further keen to understand if these regional differences in ASMR and ASPR also reflect a socio-economic bias and if so, does it reflect in a category of comorbid conditions.

Contribution of metabolic risk and hypertension in stroke based on ethnogenetic locations

When the prevalence and mortality rates of stroke and its comorbidities were grouped into three groups, namely strokes, metabolic disorders and high SBP, we find that out of the three proportional mortalities shown in figure 2, strokes group has the highest proportion (37.1%-47.2%) across all years and regions, except Oceania and America, where instead, metabolic disorders have the highest proportion (39.1%-42.2%) that is significantly higher compared to global proportion (table S4). East Asia has the highest proportional mortality for strokes among all

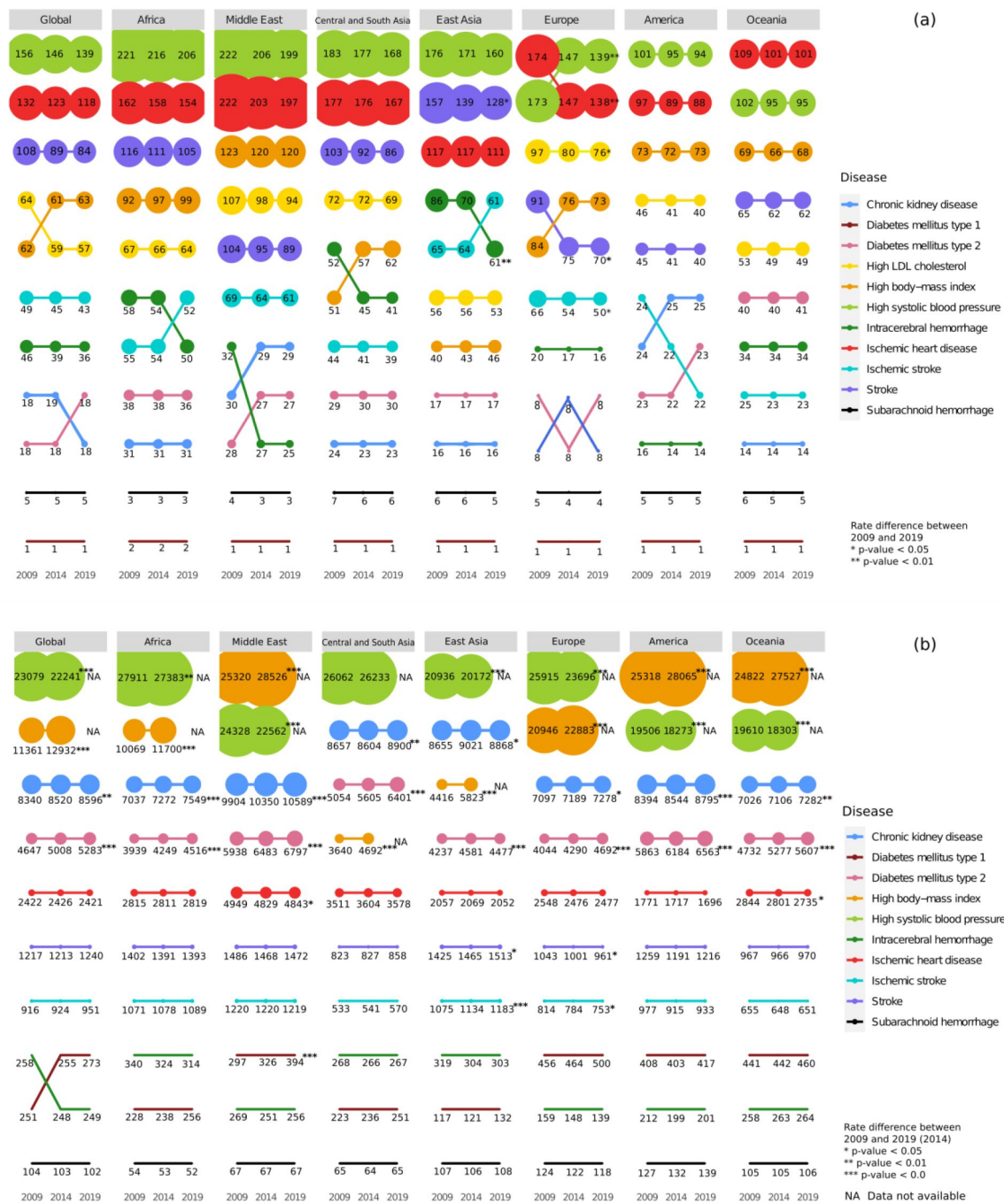


Figure 1.

Regional (a) mortality rates and (b) prevalence rates for Stroke, its subtypes and comorbid factors.

The figure shows the age-standardized mortality and prevalence rates per 100,000 people for Stroke, its subtypes and its comorbid factors in 2009, 2014 and 2019. The size of the points indicates the rate and position indicates rank.

	CKD			High BMI		
Region	2019	2009	2009-2019 EAPC	2019	2009	2009-2019 EAPC
Global	18.29 (19.6, 16.72)	18.41 (19.22, 17.1)	-0.07 (-4.32, 4.37)	62.59 (89.13, 39.92)	61.66 (90.2, 37.44)	0.16 (-2.2, 2.57)
Africa	30.58 (27.11, 34.05)	31.18 (28.37, 33.99)	-0.12 (-3.41, 3.27)	98.83 (64.77, 136.6)	91.64 (58.6, 130.04)	0.88 (-1.02, 2.82)
Central & South Asia	22.74 (17.68, 27.81)	23.72 (18.93, 28.5)	0.24 (-4.07, 3.73)	62.07 (40.97, 83.17)	51.31 (30.2, 72.47)	2.0 (-0.5, 4.56)
East Asia	15.8 (11.17, 20.42)	16.22 (12.1, 20.34)	-0.38 (-4.9, 4.36)	46.41 (36.68, 56.14)	39.76 (32.9, 46.61)	1.45 (-1.39, 4.38)
Europe	8.18 (7.06, 9.3)	8.19 (7.1, 9.29)	0.11 (-6.17, 6.81)	73.34 (60.31, 86.36)	84.45 (69.2, 99.71)	-1.42 (-3.49, 0.7)
Middle East	28.68 (22.76, 34.59)	29.75 (22.4, 37.14)	-0.46 (-3.85, 3.06)	120.14 (100.3, 139.9)	122.6 (98.3, 146.9)	-0.23 (-1.91, 1.48)
Oceania	13.71 (9.67, 17.74)	13.6 (9.16, 18.04)	0.17 (-4.76, 5.36)	67.52 (41.1, 93.93)	69.2 (42.2, 96.19)	-0.28 (-2.53, 2.02)
America	24.95 (22.85, 26.81)	23.83 (22.22, 24.68)	0.48 (-3.24, 4.34)	72.83 (48.62, 97.9)	73.34 (49.02, 99.92)	-0.01 (-2.17, 2.23)
	High LDL			High SBP		
Region	2019	2009	2009-2019 EAPC	2019	2009	2009-2019 EAPC
Global	56.51 (73.62, 41.83)	63.9 (82.9, 47.71)	-1.29 (-3.65, 1.13)	138.88 (155.7, 121.3)	156.22 (174.7, 137.3)	-1.23 (-2.74, 0.31)
Africa	64.39 (45.03, 86.13)	67.15 (48.42, 88.17)	-0.34 (-2.6, 1.98)	206.18 (177.4, 234.2)	221.26 (196.2, 247.2)	-0.64 (-1.9, 0.63)
Central & South Asia	68.91 (45.31, 92.51)	72.3 (45.6, 98.99)	-0.46 (-2.64, 1.77)	167.69 (129.1, 206.3)	183.48 (140.3, 226.6)	-0.84 (-2.23, 0.57)
East Asia	53.44 (46.16, 60.71)	56.11 (48.82, 63.4)	-0.68 (-3.15, 1.82)	160.36 (130.6, 190.1)	176.4 (146.7, 206.1)	-1.1 (-2.51, 0.33)
Europe	75.53 (57.71, 93.34)	96.66 (74.4, 119.0)	-2.53 (-4.51, -0.51)	138.88 (111.6, 166.2)	173.48 (139.1, 207.9)	-2.26 (-3.73, -0.76)
Middle East	94.43 (75.03, 113.8)	107.43 (88.6, 126.3)	-1.3 (-3.14, 0.57)	198.61 (162.8, 234.4)	222.34 (187.2, 257.5)	-1.16 (-2.43, 0.13)
Oceania	48.92 (33.56, 64.27)	53.34 (39.4, 67.27)	-0.92 (-3.51, 1.74)	94.63 (62.2, 127.06)	102.14 (70.5, 133.76)	-0.81 (-2.68, 1.09)
America	40.44 (30.0, 52.53)	45.86 (34.22, 59.38)	-1.24 (-4.05, 1.64)	93.91 (80.49, 105.8)	101.2 (87.28, 114.1)	-0.7 (-2.57, 1.21)
	IHD			ICH		
Region	2019	2009	2009-2019 EAPC	2019	2009	2009-2019 EAPC
Global	117.95	131.77	-1.17	36.04	45.92	-2.53

Table 1.

EAPC from 2009 to 2019 of age-standardized mortality rates of Stroke and its comorbid conditions.

ASMR per 100,000 for Stroke and its comorbid conditions for 2009 and 2019, as well as EAPC from 2009 to 2019 is show. 95% uncertainty interval is shown in paranthesis, statistically significant intervals are highlighted in bold..

	(125.9,107.8)	(138.3,122.4)	(-2.81, 0.5)	(38.67,32.98)	(48.45,43.07)	(-5.37, 0.39)
Africa	154.04 (132.6,175.4)	162.34 (146.4,180.7)	-0.45 (-1.91, 1.04)	49.82 (43.07,57.02)	58.06 (51.19,65.11)	-1.45 (-3.93, 1.09)
Central & South Asia	167.39 (115.8,219.0)	176.75 (118.3,235.2)	-0.51 (-1.91, 0.92)	41.45 (32.34,50.55)	51.57 (37.19,65.94)	-2.13 (-4.8, 0.62)
East Asia	110.93 (94.7,127.17)	117.17 (100.7,133.7)	-0.76 (-2.47, 0.97)	61.2 (49.06,73.33)	85.51 (70.7,100.37)	-3.54 (-5.65, -1.38)
Europe	138.19 (105.5,170.8)	174.31 (134.8,213.8)	-2.37 (-3.85, -0.88)	15.7 (12.25,19.15)	20.31 (15.85,24.77)	-2.46 (-6.77, 2.04)
Middle East	197.4 (154.9,239.9)	221.61 (178.7,264.5)	-1.14 (-2.41, 0.16)	24.94 (15.45,34.42)	31.66 (19.43,43.89)	-2.445 (-5.8, 1.03)
Oceania	100.75 (65.96,135.6)	109.14 (77.5,140.7)	-0.86 (-2.67, 0.99)	34.32 (12.57,56.07)	34.25 (12.46,56.04)	-0.056 (-3.2, 3.19)
America	87.51 (79.07,93.31)	97.5 (89.02,102.0)	-1.06 (-2.98, 0.91)	14.06 (12.97,15.03)	15.95 (15.05,16.68)	-1.21 (-5.93, 3.74)
	IS			SAH		
Region	2019	2009	2009-2019 EAPC	2019	2009	2009-2019 EAPC
Global	43.5 (46.8, 39.08)	49.24 (52.21,44.75)	-1.3 (-3.99, 1.47)	4.66 (5.17, 4.13)	5.34 (6.2, 4.57)	-1.29 (-9.21, 7.33)
Africa	52.05 (45.89,58.59)	54.74 (48.9, 60.76)	-0.43 (-2.94, 2.14)	2.73 (1.62, 4.97)	3.27 (1.9, 5.95)	-1.71 (-11.75, 9.48)
Central & South Asia	39.2 (28.7, 49.75)	44.32 (31.11,57.53)	-0.99 (-3.88, 1.95)	5.77 (4.42, 7.12)	7.15 (5.05, 9.26)	-2.16 (-9.13, 5.34)
East Asia	61.33 (50.37,72.28)	64.96 (54.8, 75.11)	-0.734 (-3.04, 1.61)	5.14 (4.66, 5.62)	6.05 (5.45, 6.65)	-1.66 (-9.11, 6.4)
Europe	50.36 (38.22,62.51)	65.67 (49.49,81.85)	-2.72 (-5.14, -0.25)	4.16 (3.55, 4.78)	4.84 (4.08, 5.6)	-1.3 (-9.74, 7.93)
Middle East	61.43 (49.71,73.15)	68.72 (57.62,79.81)	-1.17 (-3.44, 1.15)	2.91 (2.0, 3.83)	3.74 (2.82, 4.67)	-2.39 (-11.73,8.14)
Oceania	22.56 (17.61,27.52)	24.92 (20.87,28.98)	-1.04 (-4.81, 2.89)	5.27 (3.32, 7.21)	5.61 (3.57, 7.64)	-0.64 (-8.31, 7.68)
America	21.69 (18.8, 23.4)	23.96 (21.31,25.49)	-0.99 (-4.83, 2.99)	4.57 (4.16, 4.9)	4.81 (4.47, 5)	-0.45 (-8.72, 8.55)
	Stroke			T2D		
Region	2019	2009	2009-2019 EAPC	2019	2009	2009-2019 EAPC
Global	84.19 (90.15,76.76)	100.5 (105.4,93.24)	-1.85 (-3.76, 0.1)	18.49 (19.66,17.18)	18.23 (18.97,17.12)	0.21 (-4.07, 4.69)
Africa	104.6 (93.07,116.9)	116.07 (104.7,127.9)	-0.97 (-2.71, 0.81)	36.45 (33.0, 40.01)	37.5 (34.54, 40.3)	-0.24 (-3.24, 2.85)
Central & South Asia	86.42 (67.06,105.8)	103.04 (75.1,130.94)	-1.63 (-3.53, 0.3)	29.61 (24.29,34.93)	28.54 (23.45,33.63)	0.62 (-2.83, 4.17)
East Asia	127.66 (104.9,150.5)	156.52 (132.0,181.0)	-2.2 (-3.73, -0.64)	17.45 (9.53, 25.37)	16.52 (9.67, 23.37)	0.59 (-3.85, 5.24)
Europe	70.22 (54.79,85.65)	90.82 (70.3,111.34)	-2.6 (-4.65, -0.5)	8.26 (7.03, 9.48)	8.46 (6.95, 9.96)	0.09 (-6.19, 6.78)
Middle East	89.28 (70.7,107.87)	104.12 (84.6,123.63)	-1.59 (-3.44, 0.3)	27.43 (19.25, 35.6)	28.38 (18.53,38.22)	-0.38 (-3.86, 3.22)

Table 1. (continued)

Oceania	62.15 (34.12,90.18)	64.78 (37.63,91.92)	-0.47 (-2.79, 1.9)	41.29 (15.02,67.55)	40 .0 (14.19,65.81)	0.27 (-2.65, 3.27)
America	40.33 (36.24, 43.1)	44.72 (40.98,46.98)	-1.01 (-3.83, 1.9)	22.55 (20.65,24.08)	22.89 (21.35,23.69)	-0.08 (-3.96, 3.97)
T1D						
Region	2019	2009	2009-2019 EAPC	-	-	-
Global	0.98 (1.17, 0.85)	1.03 (1.22, 0.88)	-0.45 (-17.5,20.07)	-	-	-
Africa	1.59 (1.24, 1.92)	1.69 (1.29, 2.14)	-0.57 (-14.01, 14.9)	-	-	-
Central & South Asia	1.34 (1.09, 1.6)	1.4 (1.09, 1.71)	-0.33 (-14.93, 16.8)	-	-	-
East Asia	0.91 (0.33, 1.49)	0.98 (0.39, 1.56)	-1.17 (-18.6, 20.01)	-	-	-
Europe	0.51 (0.42, 0.61)	0.59 (0.49, 0.69)	-1.57 (-24.09, 27.6)	-	-	-
Middle East	1.05 (0.8, 1.3)	1.27 (0.97, 1.57)	-2.26 (-17.89, 16.3)	-	-	-
Oceania	1.06 (0.52, 1.6)	1.06 (0.53, 1.59)	-0.26 (-16.9, 19.74)	-	-	-
America	1.04 (0.8, 1.29)	1.1 (0.87, 1.37)	-0.27 (-16.89, 19.7)	-	-	-

Table 1. (continued)

	CKD			High BMI		
Region	2019	2009	2009-2019 EAPC	2016	2009	2009-2016 EAPC
Global	8596.21 (8015.74, 9125.28)	8340.38 (7792.87, 8846.68)	0.34 (0.13, 0.54)	13627.48 (14742.38, 12594.1)	11360.96 (11989.37, 10745.18)	2.63 (2.35, 2.91)
Africa	7548.86 (7063.27, 8012.72)	7037.32 (6575.34, 7477.98)	0.71 (0.49, 0.93)	12418.08 (9882.53, 14953.64)	10068.8 (7764.52, 12373.08)	3.04 (2.75, 3.34)
Central & South Asia	8900.17 (8429.97, 9370.37)	8656.77 (8113.18, 9200.36)	0.33 (0.13, 0.54)	5191.21 (3289.67, 7092.74)	3639.99 (2090.94, 5189.04)	5.2 (4.72, 5.69)
East Asia	8868.46 (8227.29, 9509.63)	8655.32 (8120.05, 9190.6)	0.27 (0.07, 0.47)	6471.83 (5527.54, 7416.12)	4416.3 (3734.86, 5097.74)	5.6 (5.17, 6.04)
Europe	7277.72 (6612.97, 7942.47)	7096.87 (6502.14, 7691.6)	0.25 (0.03, 0.47)	23696.85 (23004.53, 24389.17)	20946.03 (20353.15, 21538.91)	1.78 (1.57, 1.98)
Middle East	10589.31 (9997.33, 11181.29)	9904.13 (9402.68, 10405.57)	0.69 (0.51, 0.88)	29703.7 (26783.51, 32623.9)	25320.15 (22564.8, 28075.51)	2.36 (2.17, 2.55)
Oceania	7282.16 (6638.89, 7925.43)	7025.88 (6430.44, 7621.32)	0.39 (0.17, 0.62)	28663.27 (26270.75, 31055.79)	24822.02 (22441.51, 27202.53)	2.07 (1.89, 2.26)
America	8795.43 (8257.8, 9295.57)	8394.13 (7864.71, 8889.84)	0.52 (0.31, 0.72)	29195.14 (27054.8, 31335.48)	25317.62 (23333.24, 27302.01)	2.05 (1.87, 2.24)
	High SBP			IHD		
Region	2015	2009	2009-2015 EAPC	2019	2009	2009-2019 EAPC
Global	22078.6 (24798.17, 19573.65)	23078.95 (24774.74, 21431.11)	-0.74 (-0.98, -0.49)	2421.02 (2180.5, 2692.65)	2422.21 (2185.13, 2688.5)	-0.01 (-0.39, 0.37)
Africa	27269.91 (26515.46, 28024.36)	27910.66 (27337.87, 28483.45)	-0.39 (-0.61, -0.16)	2819.42 (2580.09, 3098.08)	2814.78 (2584.93, 3072.69)	0.02 (-0.33, 0.37)
Central & South Asia	26256.46 (25139.35, 27373.58)	26062.04 (25049.67, 27074.4)	0.12 (-0.11, 0.35)	3577.7 (3326.28, 3829.11)	3510.51 (3256.78, 3764.25)	0.18 (-0.13, 0.49)
East Asia	19997.47 (18656.73, 21338.2)	20935.67 (19829.41, 22041.94)	-0.76 (-1.02, -0.5)	2052.09 (1817.64, 2286.54)	2056.98 (1821.18, 2292.77)	-0.01 (-0.43, 0.4)
Europe	23278.69 (21812.71, 24744.67)	25915.06 (24642.41, 27187.72)	-1.77 (-2, -1.54)	2476.75 (2203.31, 2750.18)	2548.31 (2267.8, 2828.82)	-0.3 (-0.67, 0.08)

Table 2.

EAPC from 2009 to 2019 of age-standardized prevalence rates of Stroke and its comorbid conditions.

ASPR per 100,000 for Stroke and its comorbid conditions for 2009 and 2019, as well as EAPC from 2009 to 2019 is show. 95% uncertainty interval is shown in paranthesis, statistically significant intervals are highlighted in bold.

Middle East	22293.46 (20587.65, 23999.28)	24327.72 (23042.57, 25612.87)	-1.48 (-1.72, -1.24)	4843.02 (4243.46, 5442.58)	4949.35 (4386.28, 5512.41)	-0.27 (-0.54, -0.003)
Oceania	18081.14 (15851.15, 20311.13)	19610.27 (18278.28, 20942.26)	-1.34 (-1.61, -1.08)	2734.98 (2611.03, 2858.93)	2843.93 (2697.13, 2990.73)	-0.43 (-0.79, -0.08)
America	18041.91 (16571.13, 19512.69)	19505.67 (17874.04, 21137.3)	-1.29 (-1.56, -1.02)	1695.56 (1530.76, 1871.92)	1770.96 (1602.8, 1955.71)	-0.46 (-0.91, -0.01)
	ICH			IS		
Region	2019	2009	2009-2019 EAPC	2019	2009	2009-2019 EAPC
Global	248.77 (217.09, 281.43)	257.65 (226.36, 289.73)	-0.4 (-1.57, 0.79)	950.97 (849.82, 1064.06)	916.46 (827.21, 1011.45)	0.43 (-0.18, 1.05)
Africa	314.25 (281.2, 349.75)	340.25 (305.47, 377.42)	-0.88 (-1.9, 0.15)	1089.33 (984.73, 1198.86)	1071.4 (971.23, 1174.89)	0.18 (-0.39, 0.75)
Central & South Asia	267.03 (223.81, 310.25)	268.32 (214.19, 322.45)	-0.05 (-1.19, 1.1)	570.43 (480.32, 660.53)	533.37 (437.92, 628.82)	0.76 (-0.04, 1.57)
East Asia	302.65 (221.3, 384.01)	319.25 (236.89, 401.6)	-0.58 (-1.64, 0.48)	1183.05 (1086.71, 1279.4)	1074.86 (1001.51, 1148.22)	1.09 (0.53, 1.65)
Europe	139.23 (120.98, 157.49)	158.58 (135.99, 181.17)	-1.44 (-2.94, 0.09)	753.15 (676.12, 830.17)	813.8 (730.34, 897.26)	-0.85 (-1.51, -0.19)
Middle East	255.65 (199.55, 311.75)	268.51 (211.97, 325.06)	-0.7 (-1.85, 0.46)	1218.88 (1060.37, 1377.4)	1220.26 (1066.3, 1374.22)	-0.07 (-0.61, 0.47)
Oceania	264.45 (113.71, 415.19)	258.3 (103.93, 412.68)	0.17 (-0.98, 1.34)	650.92 (557.27, 744.58)	655.29 (569.12, 741.47)	-0.09 (-0.82, 0.64)
America	200.52 (176.38, 226.00)	212.00 (188.08, 237.72)	-0.58 (-1.87, 0.73)	932.69 (829.99, 1041.00)	977.11 (888.38, 1068.44)	-0.4 (-1.00, 0.21)
	SAH			Stroke		
Region	2019	2009	2009-2019 EAPC	2019	2009	2009-2019 EAPC
Global	101.57 (87.13, 118.54)	103.6 (89.2, 120.53)	-0.22 (-2.05, 1.64)	1240.26 (1139.71, 1352.99)	1217.36 (1126.81, 1313.52)	0.22 (-0.31, 0.76)
Africa	52.47 (44.76, 61.46)	53.58 (45.9, 62.63)	-0.2 (-2.74, 2.39)	1393.27 (1288.31, 1503.93)	1402.18 (1303.49, 1509.44)	-0.08 (-0.57, 0.43)
Central & South Asia	65.01 (56.51, 73.52)	64.76 (54.84, 74.67)	0.05 (-2.25, 2.41)	858.5 (737.58, 979.42)	822.67 (682.76, 962.57)	0.48 (-0.16, 1.14)

Table 2. (continued)

East Asia	107.87 (72.53, 143.2)	107.03 (72.44, 141.62)	0.12 (-1.67, 1.95)	1513.1 (1390.7, 1635.49)	1425.39 (1298.41, 1552.38)	0.69 (0.2, 1.18)
Europe	118.34 (108.49, 128.2)	124.24 (112.18, 136.31)	-0.52 (-2.19, 1.18)	960.86 (861.79, 1059.92)	1042.89 (932.11, 1153.68)	-0.9 (-1.49, -0.31)
Middle East	66.69 (58.12, 75.25)	67.19 (57.51, 76.87)	-0.03 (-2.27, 2.26)	1471.6 (1292.03, 1651.17)	1485.6 (1313.34, 1657.86)	-0.18 (-0.66, 0.31)
Oceania	105.79 (85.55, 126.03)	104.66 (83.96, 125.35)	0.13 (-1.68, 1.97)	970.31 (719.9, 1220.73)	967.25 (721.78, 1212.72)	-0.0006 (-0.6, 0.6)
America	138.9 (119.01, 162.64)	127.3 (110.52, 146.72)	0.75 (-0.87, 2.4)	1215.6 (1113.69, 1328.23)	1259.25 (1171.81, 1351.47)	-0.32 (-0.85, 0.22)
	T1D			T2D		
Region	2019	2009	2009-2019 EAPC	2019	2009	2009-2019 EAPC
Global	272.54 (216.98, 336.95)	250.88 (203.63, 307.25)	0.71 (-0.45, 1.89)	5282.85 (4853.59, 5752.09)	4646.97 (4341.45, 4960.45)	1.24 (0.97, 1.51)
Africa	255.51 (201.1, 318.05)	227.8 (179.02, 286.18)	1.16 (-0.06, 2.39)	4516.3 (4096.49, 4976.22)	3939.47 (3629.16, 4276.48)	1.35 (1.06, 1.64)
Central & South Asia	250.87 (235.66, 266.09)	222.68 (211.11, 234.25)	1.12 (-0.1, 2.36)	6401.5 (5931.41, 6871.58)	5054.2 (4714.43, 5393.97)	2.18 (1.93, 2.44)
East Asia	132.14 (92.27, 172)	117.02 (75.77, 158.27)	0.97 (-0.72, 2.7)	4477.09 (4223.96, 4730.21)	4237.06 (3842.25, 4631.87)	0.68 (0.4, 0.97)
Europe	499.9 (451.46, 548.34)	458.58 (394.14, 523.02)	0.69 (-0.17, 1.56)	4691.56 (4113.82, 5269.3)	4044.18 (3599.81, 4488.54)	1.45 (1.16, 1.74)
Middle East	394.02 (354.45, 433.59)	297 (246.27, 347.72)	2.84 (1.79, 3.89)	6796.8 (5773.01, 7820.59)	5937.92 (5063.13, 6812.7)	1.3 (1.06, 1.53)
Oceania	459.51 (335.35, 583.67)	441.02 (327.93, 554.11)	0.4 (-0.48, 1.29)	5606.6 (3790.83, 7422.38)	4732.14 (3129.63, 6334.64)	1.87 (1.61, 2.14)
America	417.47 (337.43, 511.23)	408.22 (340.36, 487.84)	0.14 (-0.79, 1.07)	6563.01 (6071.37, 7036.07)	5862.85 (5515.86, 6198.91)	1.09 (0.85, 1.33)

Table 2. (continued)

regions in all three years (44.7%-47.2%). This was in sharp contrast to prevalence proportion of strokes (4.6%-9.1%), which was the least among the three groups, with the highest proportional prevalence for strokes being 8.9%-9.1% in CSA. The proportional mortality for high SBP (22.0%-30.5%) is very similar across the regions. Metabolic disorders have significantly higher proportional prevalence compared to global in MDE, Oceania and America, the highest being in America (63.9%, table S5). Asian and African regions have lowest proportional prevalence for metabolic disorders, with CSA having significantly lower proportion. However, these regions have the highest prevalence proportion for high SBP (46.6% - 54.3%), with CSA having a significantly highest proportion compared to global. On the other hand, MDE, Oceania and America has significantly lower proportional prevalence compared to global. We were further keen to understand the correlation among ASMR and ASPR of comorbid conditions among ethnogeographic regions.

Correlation among prevalence and mortality rates based on ethnogeographic region

Correlation between ASMRs and ASPRs for stroke and all comorbid conditions across each ethnogeographic locations is shown in [figure 3](#). High SBP prevalence and mortality show a strong positive correlation in CSA but a strong negative correlation in MDE. The prevalence and mortality of high BMI has a strong negative correlation in CSA and MDE populations, but a strong positive correlation in EAS. Prevalence of CKD has negative correlation with mortality rates in EAS. Prevalence of T2D has negative correlation with mortality rates in Oceania and positive correlation in America. It is interesting to note that there was not much of a correlation in mortality and prevalence rates for most of the conditions. For overall stroke, though minor correlations between various ethnicities are seen, this becomes alarmingly clear in the stroke subtypes. The correlation matrix of ASMR and ASPR of stroke and its comorbidities does reflect strong ethnogeographic distinctions, which formed the basis of further investigation on genetic basis of stroke and its comorbidities.

Ethnogeographic stratification of stroke and its comorbidities based on GWAS data

To resolve the ethnogeographic distinctions for stroke and its major comorbid conditions based on their genetic risk, we considered all GWAS loci for stroke and its major comorbid conditions, and subjected it to stratification analysis. From the GWAS loci, we observed a distinct population structure that distinguished ethnogeographic populations based on their genetic signatures ([Fig. 4](#)). For all diseases, except high BMI, the individuals clustered into five groups, each corresponding with the five super-populations from 1000 Genome project namely, African, East Asian, South Asian, European and American. For high BMI, the individuals clustered into three groups corresponding to African, East Asian, European. Though broad clustering of ancestral populations among the diseases looks similar, the proportions of ancestral populations in certain diseases vary greatly. Among Stroke, IHD and T2D risk variants, the populations structured in a similar way, while for T1D, CKD and LDL the patterns were slightly different in European and South Asian ancestry. Whereas for high SBP the major fluctuations were observed in South Asian and East Asian populations. This stratification was further explored using population-based clustering, where a similar pattern was observed in PCA plots for stroke and its comorbid conditions ([Fig. 5](#)). African population seems to be a distinct outlier for most diseases, and the East Asian comes a distant second in the cluster pattern.

Similar patterns were observed in stratification analysis after grouping the GWAS loci of stroke and its comorbidities into three groups as before, namely strokes, metabolic disorders and high SBP. The African, East Asian and South Asian populations had distinct structure in all three groups (fig. S5). These observations do indicate that the underlying genetic factors of stroke and its

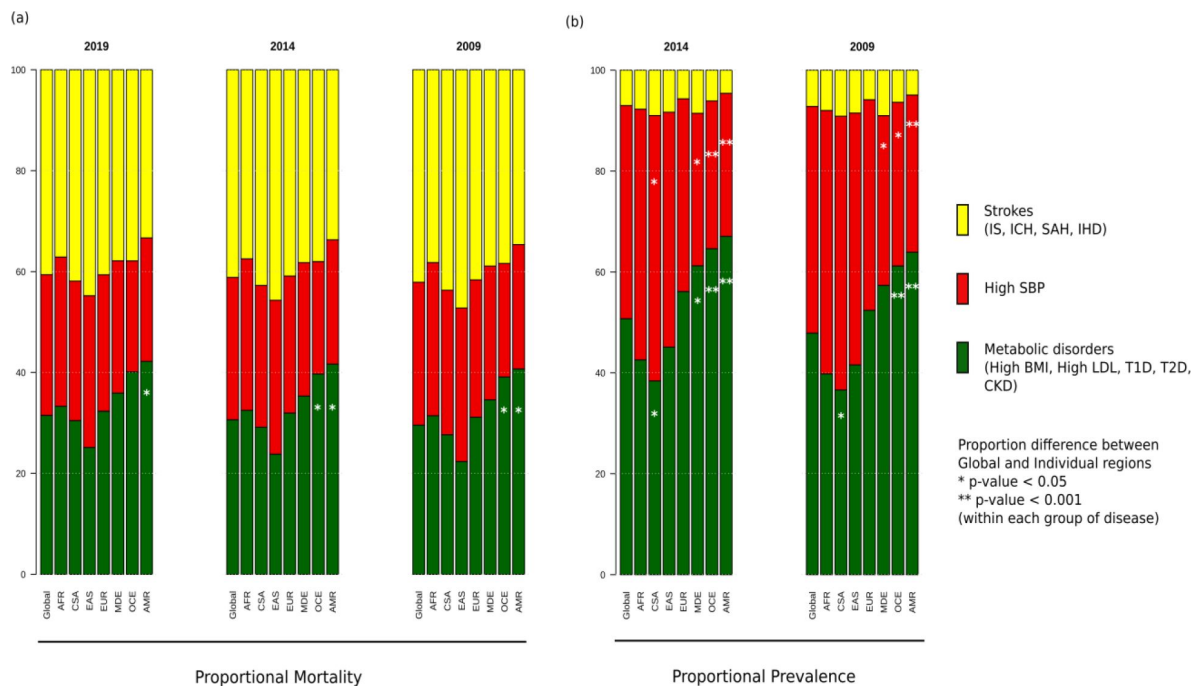


Figure 2.

Proportional (a) mortality rates and (b) prevalence rates for Strokes, High SBP and Metabolic disorders.

The figure shows the proportional mortality and prevalence for all strokes in yellow (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage and ischemic heart disease), high systolic blood pressure in red, and metabolic disorders in green (high BMI, high LDL, diabetes mellitus type 1 and 2, chronic kidney disorder). CSA - Central and South Asia, AFR - Africa, EAS - East Asia, EUR - Europe, MDE - Middle East, OCE - Oceania, AMR - America.

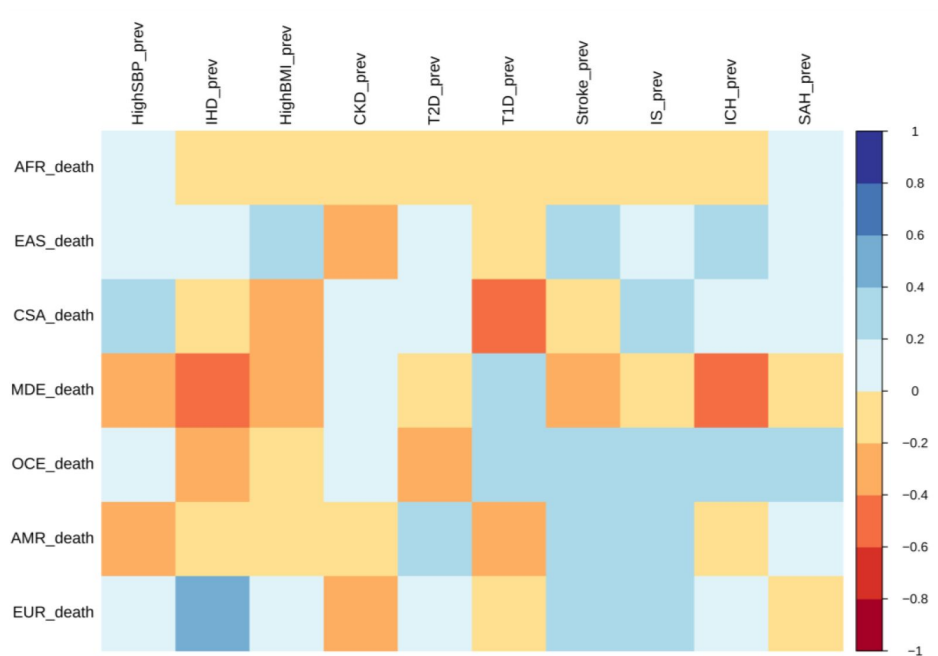


Figure 3

Correlation of mortality versus prevalence rates of Stroke, its subtypes and comorbid factors.

The figure shows the Pearson correlation coefficients of mortality rates versus prevalence rates across different continents for 2014. CSA - Central and South Asia, AFR - Africa, EAS - East Asia, EUR - Europe, MDE - Middle East, OCE - Oceania, AMR - America.

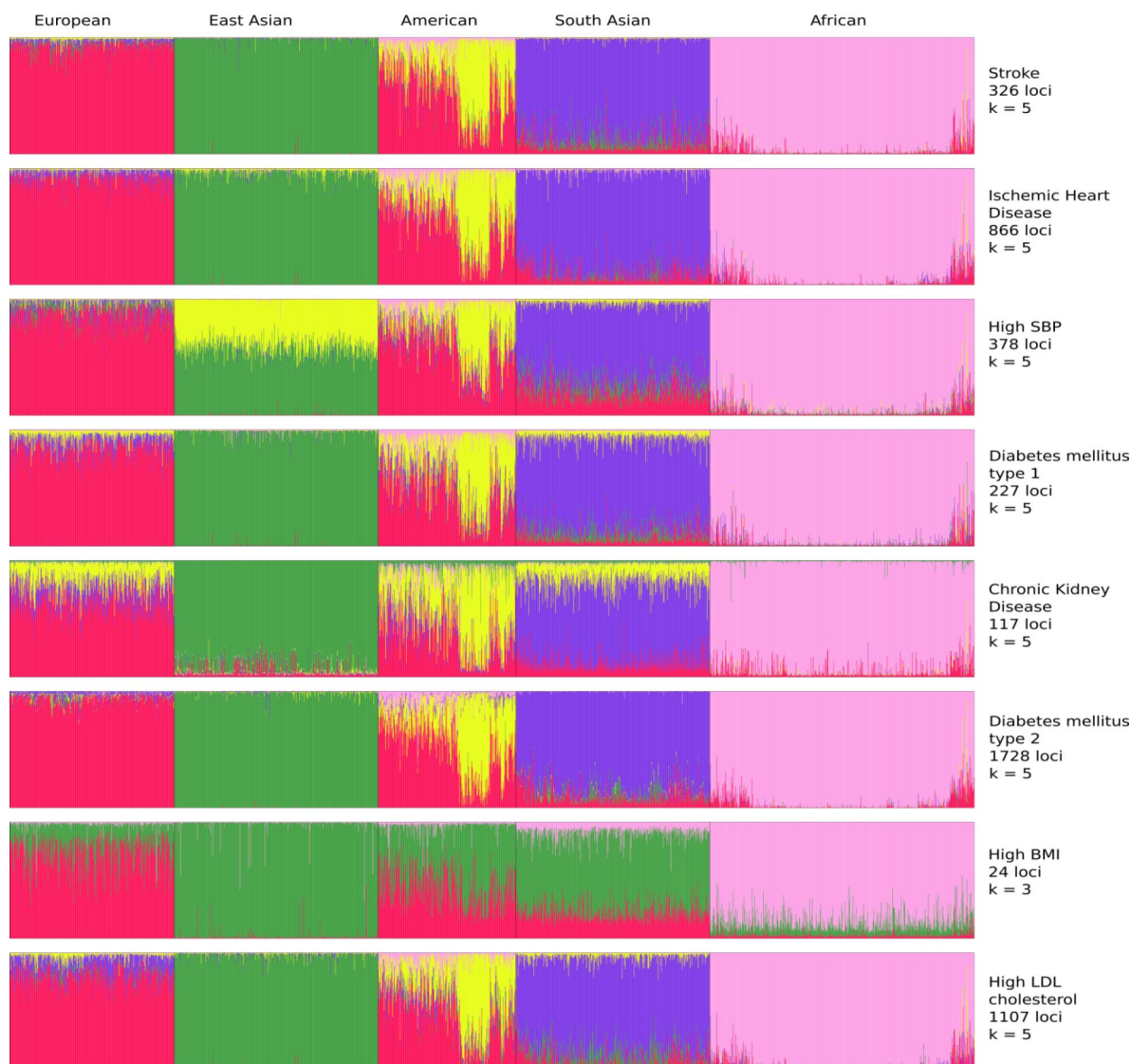


Figure 4

Population structure of risk variants for Stroke and its comorbid factors using a model-based clustering.

The proportion of ancestral populations was estimated from the genotype of risk variants of each disease in unrelated individuals from the 1000 Genomes project using a model-based clustering approach. The individuals were represented by their super-population in 1000 Genomes (African, East Asian, South Asian, European and American). The estimated ancestral populations clustered into either 5 clusters or 3 clusters (in case of BMI) represented by the different colors.

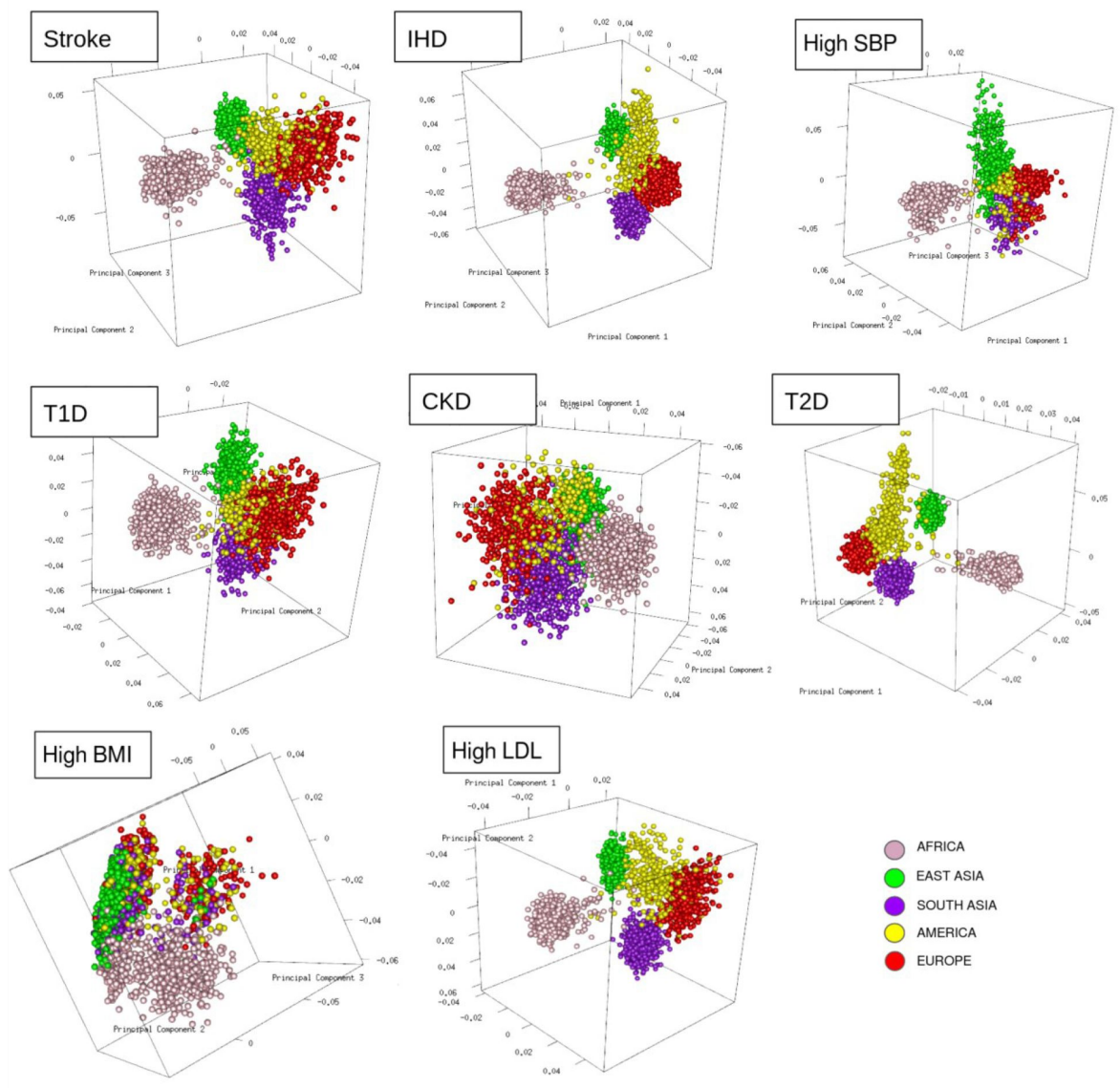


Figure 5

Clustering of risk variants for Stroke and its comorbid factors using a PCA.

The eigenvectors were estimated from the genotype of risk variants of each disease in unrelated individuals from the 1000 Genomes project using PCA clustering. The individuals were represented by their super-population in 1000 Genomes (African, East Asian, South Asian, European and American) shown in five different colors.

comorbid factors can be the real indicators of ethnogeographic patterns of risk for stroke and its comorbid conditions. However, we were further keen to understand the extent of shared and unique individual risk variants across stroke and its comorbid condition and how these unique or shared variants can help in distinguishing their relevance across ethnicities.

Shared and unique risk variants of stroke among the different ethnogenetic regions

The unique and shared individual variants across stroke and its comorbid conditions were identified from the GWAS data irrespective of ethnicity. We find majority of the risk variants were unique to a disease condition, however, several risk variants were also seen to be shared with stroke and other comorbid conditions as seen in [Figure 6](#). We were further keen to have a deeper insight into the distribution of risk variants in stroke across ethnicities. Stroke has only 55% of the risk variants common to all the five populations as seen in [figure 7](#) and table S6. Two groups of populations share the most number of variants, namely, the Africa-America-Europe-South Asia (6% of variants shared) group and the East Asia-America-Europe-South Asia (4%) group. Africa has the highest number of unique variants for stroke (6%), followed by Europe (3%).

South Asia has two unique variants for stroke, rs528002287 and rs148010464, which maps to genes PCSK6 and the intergenic region of PLA2G4A/LINC01036, respectively. The variants rs528002287 and rs148010464 are low frequency variants in South Asia with a MAF of 0.053 and 0.054, respectively. We were further keen to understand how these unique variants in South Asia are tagged to the nearby variants of different frequencies in the different ethnicities. Can the LD patterns of rare allele and common allele help in distinguishing the ethnogeographic distinction in phenotype variation. On comparison, the linkage disequilibrium (LD) pattern of low frequency variants and common variants across ethnicities showed contrasting patterns. The LD plots between the unique variants and low frequency variants tagged to it clearly demonstrated a unique LD pattern in South Asia, compared to other populations ([Figure 8](#)). Contrastingly, the LD plots of common variants tagged to the risk variant of stroke unique to South Asia showed similar LD patterns among all populations (fig. S6). These differences might also reflect unique or distinct phenotypic differences among ethnicities for risk in stroke.

Discussion

To the best of our knowledge, this is the first study that explored the burden of stroke and its comorbid conditions across regions, stratifying and distinguishing their unique features based on their genetic background extrapolated from the GWAS risk loci. The dynamics of different rates of stroke, its subtypes and comorbid factors do reflect ethnogeographic differences. Globally, the prevalence and incidence rates of stroke have increased, while mortality rates decreased with minor shifts in ranking in the last decade. Interestingly, the incidence and prevalence rank of stroke rates remain the same globally, but for mortality it ranks third, preceded only by IHD and high SBP. While the global stroke prevalence is nearly 15 times its mortality rate, prevalence of comorbid conditions such as high SBP, high BMI, CKD, T2D are alarmingly 150- to 500-fold higher than their mortality rates. These comorbid conditions can drastically affect the outcome of stroke. Interestingly, these disparities in rates get further widened when evaluated from an ethnogeographic perspective. The age-standardized prevalence of stroke in 2019 ranges from lowest in CSA (858.5/100000, 95%UI 737.6-979.4) to highest in EAS (1513.1/100000, 95%UI 1390.7-1635.5), in contrast to mortality rates, lowest in America (40.3/100000, 95%UI 36.2-43.1) and highest in EAS (127.7/100000, 95%UI 104.9-150.5).

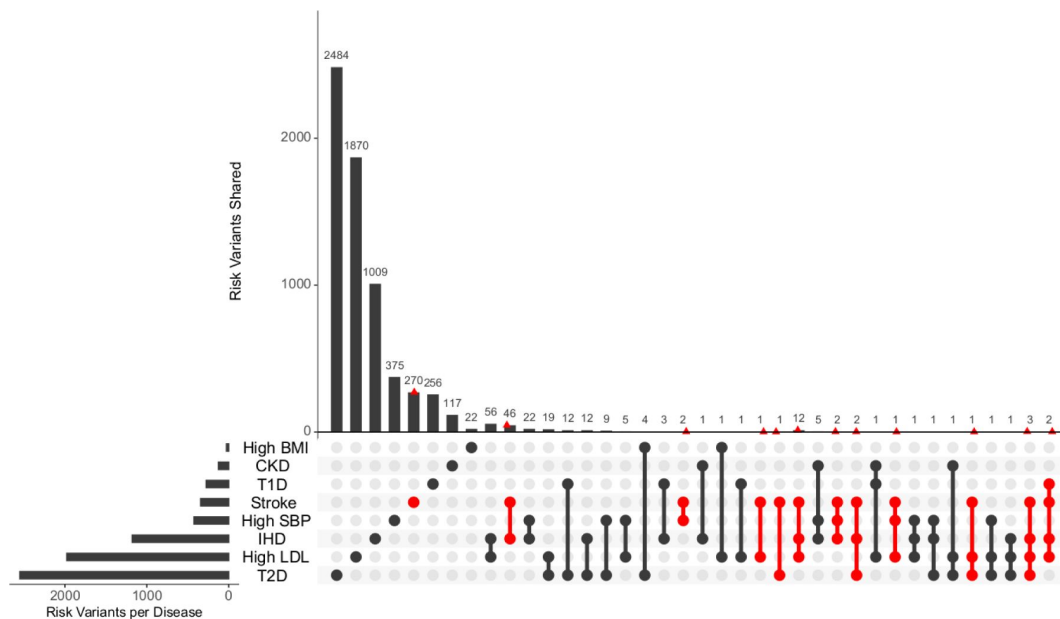


Figure 6

Distribution of unique and shared risk variants in stroke and its comorbid conditions.

The barplot shows the number of GWAS risk variants unique for stroke and its comorbidities, as well as number of GWAS risk variants shared among the different diseases. The intersection of diseases is indicated below. Intersections containing stroke are highlighted in red. The total number of GWAS risk variants considered are stroke (366), IHD (1137), High SBP (419), T2D (2227), T1D (269), CKD (125), High BMI (27) and High LDL (1734).

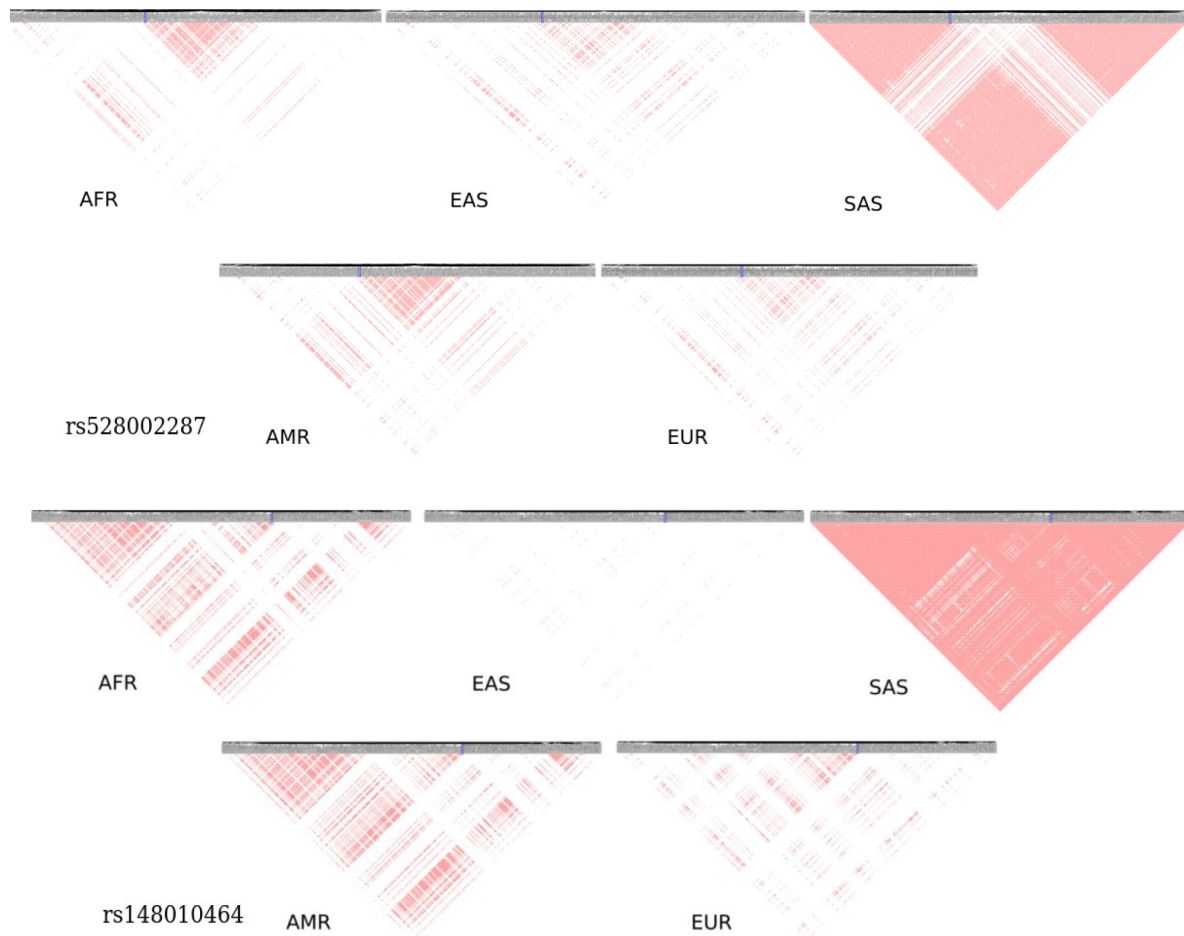


Figure 8

Linkage disequilibrium of low frequency variants proxy to risk variants of stroke unique in South Asian population.

Proxy variants with frequency less than 0.1 in 1MB region flanking the stroke risk variants unique in South Asia (a) rs528002287 and (b) rs148010464. The risk variants are marked in blue box. LD plots of variants in different 1000 Genome super-populations (AFR- Africa, EAS- East Asia, SAS – South Asia, AMR – America, EUR – Europe) are shown.

The rates of stroke, its subtypes and comorbid conditions do correlate to some extent but their ranking varies significantly. In terms of ranking, stroke ranks sixth in prevalence across all ethnogeographic locations, but ranks second in mortality in EAS and third in CSA and Africa. We find that among the considered comorbid conditions, some rank above stroke in both incidence and prevalence, however in terms of mortality, stroke ranks highest with exception to high SBP. Similarly, the ranking of the comorbid conditions also varies when the global population is stratified based on ethnogeographic locations. In the last decade, there has been tremendous development in the healthcare industry globally, but this is not reflected in the mortality or prevalence data from 2009-2019. Ranking of comorbid conditions by the rates is very crucial to identify ethnic-specific comorbid risk that can be helpful in guiding and managing stroke risk.

The changing dynamics of stroke or its comorbid conditions can be attributed to multitude of factors. Often global burden of stroke has been discussed from the point of view of socio-economic parameters. Studies indicate that half of the stroke-related deaths are attributable to poor management of modifiable risk factors^{8,9}. However, we observe that different socio-economic regions are driven by different risk factors. Considering that Europe, America, Oceania and the Middle East represent high socio-economic regions, the comorbid conditions that drive prevalence and mortality rates here seem to be more of metabolic in nature, while for South Asians, high SBP is the prominent factor. It is evident from the correlation between prevalence and mortality for stroke, its subtypes and comorbid conditions that there is an ethnic and comorbid specific correlation, which possibly does not reflect a clear socio-economic distinction. The comorbid conditions for stroke subtypes also differ to a large extent. Diabetes is a comorbid condition for stroke but not for SAH, and this risk is ethnic-specific^{10,11}. Therefore, it is very pertinent to understand the stroke risk from an ethnic view point, beyond the boundaries of socio-economic criteria, as the drivers of comorbid risk and ethnicity rely on genetic and epigenetic components. Studies reported reduction in life expectancy in 31 of 37 high-income countries, deduced to be due to COVID-19¹². However, it would be unfair to ignore the comorbid conditions which could also be the critical determinants for reduced life expectancy in these countries.

Stroke has a complex etiology, which is further influenced by its comorbid conditions and this impacts its phenotypic variability. A strong genetic risk drives both stroke and its comorbid conditions. Genetic risk variants for diabetes, cardiovascular disease, diabetic retino- and nephropathies, hypertension, inflammation and kidney diseases have been reportedly shown to have strong ethnogenetic variation¹³. Implications of ethnogenetic differences were evident when GWAS genes for stroke and all studies comorbid conditions were used to stratify the 1000 genome super-populations. We observed that the GWAS risk loci for stroke and its comorbid conditions like high BMI, high LDL, high SBP, T2D, T1D, and CKD could stratify the super-populations based on its ethnogenetic considerations. Fluctuations in genetic structure of stroke and its comorbid conditions signify the impact of ethnic variations on mortality and prevalence rates. Stroke accounts for approximately 20% of deaths in diabetics^{14,15}. Diabetics and pre-diabetics, and the duration of diabetes have been reported to have increased risk of stroke, which gets aggravated in African-Americans^{14,15}. As stroke and its comorbid conditions are heavily influenced by lifestyle, high-income countries showed evidence of metabolic disorders being the major cause of concern for both prevalence and mortality. Similar observation in a UK biobank cohort study on stroke suggests that genetic and lifestyle factors were independently associated with incident stroke, which emphasizes the benefit of entire populations adhering to a healthy lifestyle, independent of genetic risk¹⁶.

Metabolic risk variations could also be a reflection of their underlying genetic differences. Significant differences among ethnicities in metabolism of various macromolecules have been reported¹⁷. Genetic variations demonstrate inter-ethnic differences in LDL levels resulting in differential impact on dyslipidemia¹⁸. A meta-analysis on European, East Asian and African-American ethnicities revealed that common variants of *CDH13* and *ADIPOQ* regulate adiponectin levels, an important component of BMI indicator¹⁹. *ALDH2**504Lys allele has been reported to

be associated with high BMI, increased tolerance of alcohol, high SBP, and decreased high-density lipoprotein (HDL) in East Asians^{20,21}. MEGASTROKE consortium on stroke and its comorbid factors reported five variants associated with blood pressure, two with LDL cholesterol and reported that all stroke subtypes were associated with a Genetic Risk Score (GRS) for high SBP²². A study on IHD, T2D in European populations with different health-care systems, and local population substructures reported Polygenic risk score (PRS) with similar accuracy across Europeans, to a lesser extent to South and East Asian populations, and very poor transferability for Africans²³.

Even stroke subtypes show a strong ethnic variation^{22,24}. While *COL4A1* and *COL4A2* were common denominators for most of the stroke subtypes, HDL was inversely associated with small vessel stroke²⁵. The INTERSTROKE study on stroke subtypes reported that among comorbid factors, high SBP was significantly associated with ICH and diabetes, cardiac issues, and apolipoproteins with ischemic stroke²⁶. Ischemic stroke associated with ApoB/ApoA1 ratio had higher (67.6%) population attributable fraction (PAF) in Southeast Asia compared to Western Europe, North America, and Australia (24.8%), while ischemic stroke associated with atrial fibrillation had lower PAF in South Asia (3.1%) compared to the rest (17.1%)²⁶. Emerging studies like novel ethnic specific genetic variants, such as SUMOylation pathway in Indians²⁷, *SFXN4* and *TMEM108* in Africans²⁸ indicate the involvement of different pathways among different ethnicities in stroke. The A allele of c.*84G>A loci in *CETP* gene was found to be a risk factor for IHD in South Asians²⁹. High SBP was found to be a risk factor in all major stroke subtypes except lobar ICH³⁰. Therefore, identifying differential risk in different ethnicities for stroke and its subtypes, and its impact on comorbid conditions might also indicate different treatment modalities which can minimize adverse metabolic side effects.

Identifying the pattern of genetic variation is critical in distinguishing stroke and its endophenotypic variations. The risk variants rs528002287 (locus 15q26.3) in *PCSK6* and rs148010464 (locus 1q31.1) an intergenic variant in *PLA2G4A/LINC01036* for stroke were unique to South Asia, and were found to be associated with cardioembolic stroke and small vessel stroke in South Asians²⁷. A recent INTERSTROKE study reported association of short sleep duration with increased risk for stroke to be highest in the South Asian ethnicity (OR 9.13, 95% CI 5.86-14.66)⁴³. Decreased sleep quantity and quality has been reported to increase blood pressure⁴⁴, prevalence for which was found to be highest for South Asians in our study. These observations are interesting as *PCSK6* is known to regulate sodium homeostasis and thereby maintaining diastolic blood pressure^{31,32}. Reports also indicate 2.34 fold difference in the expression of *PCSK6* during maintenance phase of hypertension³³. *PCSK6* has also been reported to be involved in processing of precursors of Melanin Concentrating hormone (MCH) under certain conditions⁴⁵. MCH is known to play a central role in promoting and stabilizing sleep^{46,47}. In insomnia patients, *PLA2G4A* was reported to be upregulated by 1.88 fold after improvement in sleep⁴⁸. In sleep deprived mice, glycolytic pathway and lipid metabolism was upregulated and expression of *PLA2G4A* was downregulated⁴⁹. These observations are interesting as *PLA2G4A* is known to play a role in the metabolism of phospholipids, production of lipid mediators and the release of arachidonic acid (AA)^{35,36}. AA is involved in signaling pathways of metabolic processes like release of insulin and glucose disposal³⁷⁻³⁹. *PLA2G4A* also plays a role in the production of pro-thrombotic TXA2 and thus, inhibition of *PLA2G4A* can reduce platelet aggregation and thromboembolism⁴⁰. Thus, the risk of unique genetic variants in *PCSK6* and *PLA2G4A* in South Asian ancestry may indicate a unique endophenotype for stroke, which might also indicate the influence of underlying risk variants for comorbid conditions. E.g. *PLA2G4A* in metabolic processes.

GWAS has yielded numerous common risk alleles that are associated with various human phenotypes^{50,51}. Since the rationale for GWAS is the ‘common disease, common variant’ hypothesis, it has been able to identify only those common variants with a moderate effect on the associated trait and thus, these identified variants only explain a small proportion of the

heritability of the trait. One of the major conclusions from the 1000 Genomes Project was that most variations in the human genome are rare and unique to specific sub-populations^{52,53}. From an evolutionary point of view, alleles with strong effects that are detrimental will be controlled by purifying selection keeping its frequency low. Hence, rare and low frequency variants might be variants with large effects on traits⁵⁴. Examples of genes like *ABCA1*, *PCSK9* and *LDLR*^{55,56}, which carries both common variants with moderate effects as well as rare variants with large effect for lipid levels indicate that genes can contain both types of variants associated with a complex trait. Using this logic, we were keen to identify the influence of common and rare variants in stroke and its comorbid conditions and their pattern of LD in distinguishing ethnic specific risk.

While we observe majority of the GWAS variants associated with stroke are common variants, a minority of these are low frequency variants with below 10% frequency. The alternate alleles of these variants were found to be present only in specific super-populations of 1000 Genomes, while the variants are monoallelic in the other super-populations. This difference among populations gets further enhanced when we look at the LD patterns of these low frequency variants with other low frequency variants which are in proxy. Distinct LD blocks with these unique rare variants present in one super-population was seen to be absent in other populations. On the other hand, LD patterns of common variants (frequency greater than 10%) in the same regions shows similar LD patterns for all populations. Thus, the rare variant hypothesis could explain a significant proportion of the differences in burden of stroke seen across populations. Such genes identified could be possible candidate genes for identifying rare and low frequency variants that could play a role in the heritability of stroke and its comorbid factors.

Conclusions

The dynamics of incidence, prevalence and mortality rates of stroke and its subtypes along with its comorbid risk factors reflect strong ethnogeographic differences. Our work highlights that these ethnogeographic differences for stroke and its comorbid conditions need to be evaluated and stratified based on their ethnogenetic background. Genetic variables should be considered as primary evidence as they define the threshold for biochemical, metabolomic or epigenetic variables. The different socio-economic regions are driven by different risk factors of stroke and low frequency variants could be playing a role in the differences in burden of stroke seen in the different regions. Identifying population specific unique variants for stroke and its comorbid conditions might refine the drivers for endophenotypic variations for stroke risk. We would like to suggest that integrating public health genomics and articulating it with comorbid conditions for stroke should be considered crucial irrespective of the economic status, as both lower and higher socio-economic regions have different drivers of stroke risk.

Methods

Data sources

We obtained age-standardized incidence rates (ASIRs), age-standardized prevalence rates (ASPRs) and age-standardized mortality rates (ASMRs) for a total of eight diseases and three disease conditions in 204 countries, for the years 2009 to 2019 using the GBD Results Tool (<https://vizhub.healthdata.org/gbd-results/>)⁵⁸ and from NCD Risk Factor Collaboration (NCD-RisC, <https://ncdrisc.org/>) study^{59,60} in November 2021. GBD codes for the selected diseases were B.2.2 (Ischemic heart disease, IHD), B.2.3 (Stroke), B.2.3.1 (Ischemic stroke, IS), B.2.3.2 (Intracerebral hemorrhage, ICH), B.2.3.3 (Subarachnoid hemorrhage, SAH), B.8.1.1 (Diabetes mellitus type 1, T1D), B.8.1.2 (Diabetes mellitus type 2, T2D) and B.8.2 (Chronic kidney disease, CKD). Three disease

conditions, which are also comorbid factors of stroke, were also selected, high systolic blood pressure (SBP) (>110-115 mmHg), high body mass index (BMI > 23.0 kg/m²), and high LDL cholesterol. For these, ASMRs in 204 countries, as well as global rates for 2009 to 2019 were obtained using the GBD Results Tool, and age-standardized prevalence percentages in 204 countries for the years 2009 to 2016 (data for 2017 to 2019 was not available) were obtained using NCD-Risc website (<https://ncdrisc.org/>)^{59,60}. Global crude rates and age-standardized incidence, prevalence and mortality rates were obtained from GBD and NCD for all the diseases and disease conditions (Figure S1, Table S1). GBD 2019 and NCD-RisC study compiled with the GATHER Guidelines.

Spatio-temporal trend analysis and estimated annual percent change

The 204 countries were grouped into eight geographic regions namely Global, America (AMR), Europe (EUR), Middle East (MDE), Africa (AFR), Central Asia & South Asia (CSA), East Asia (EAS), and Oceania (OCE), based on ethnicity (Table S7, Figure S2). The prevalence percentages were converted into ASPRs for each disease condition. ASMRs and ASPRs for each region was obtained using Bayesian model averaging of linear regression models with Markov chain Monte Carlo sampling. BIC was the model selection criteria. Poisson distribution with global rates as lambda was the prior distribution on the models. The population of each country was used as weights. 10000 draws from the posterior distribution of model parameters were used to obtain the point estimates (mean of the draws) and 95% uncertainty intervals (2.5th to 97.5th percentiles of the posterior distributions) of mortality and prevalence rates for each region for years 2009 to 2019. Rate estimates presented in this paper are age-standardized rates per 100,000 population.

The ASMRs and ASPRs thus obtained for the different diseases in each region were subjected to a temporal rank analysis for 2009, 2014, and 2019 using custom perl scripts and change in the trend was plotted as a bump plot. The size and position of the points indicates the rate and rank respectively. To quantify the temporal trends, estimated annual percentage change (EAPC) was modeled using Poisson regression using a generalized linear model for the log-transformed rates: $\log(y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_p x_p$, where y is the age-standardized rate, x_i are the calendar years, β_i are the rate trends. Under the assumption of linearity of log of age-standardized rate with time, $EAPC = 100 \times \exp(\beta^\wedge) - 1$. The 95% uncertainty interval is calculated as $CI(EAPC) = \beta \pm (Z_{(1-\alpha)/2}) \times SE$, where α is the confidence level, SE is the standard error of $\beta^\wedge$.

EAPC for ASMRs and ASPRs were calculated for the time period 2009 to 2019 (**table 1** [↗](#) and **2** [↗](#)). EAPC for high SBP prevalence was calculated from 2009 to 2015 and for high BMI prevalence from 2009 to 2016. EAPC was considered statistically significant if the uncertainty interval of EAPC did not cross zero. Statistical significance of spatio-temporal difference in rates was calculated using chi-square test by assuming the rate to be under Poisson distribution. 2019 ASMRs (or ASPRs) in each region were compared with global ASMR (or ASPR) to compare change over locations and with 2009 ASMRs (ASPRs) to compare change over time. 2014 ASPRs were used when 2019 data was not available. P-values (two-sided) for ASMRs and ASPRs are shown in table S3 and S4, respectively. Chi-square tests were done using Open Source Epidemiologic Statistics for Public Health (www.openepi.com/Menu/OE_Menu.htm [↗](#)). The relation between ASMRs and ASPRs of each region was measured using Pearson correlation. For correlation, we considered the data of 2014 due to the complete spectrum of data availability. All analysis, unless specified, was done using R Statistical Software (version 4.1.2) with packages BAS, Rcan, corrplot, dplyr and ggplot2.

Proportional mortality and prevalence

The diseases were classified into three categories as stroke (IS, ICH, SAH and IHD), metabolic disorders (High BMI, High LDL, T2D, CKD, and T1D) and high SBP. To determine the proportion of each category in a region, total ASMRs were scaled to 100 for all three years. The same was done for ASPRs (high LDL cholesterol data was not available). Statistical significance of difference in

proportions was calculated using one-sample test for binomial proportion using normal-theory method. The proportion mortality in each category was compared in a pairwise manner with global as well other regional proportions to calculate the two-sided p-value. The same was done for proportional prevalence. P-values for proportional mortality and prevalence are shown in tables S5 and S6, respectively. Proportion comparison were done using Open Source Epidemiologic Statistics for Public Health (http://www.openepi.com/Menu/OE_Menu.htm [↗](#)).

Population Structure Analysis

For evaluating the ethnogenetic perspective of stroke and its comorbid conditions we considered the risk variants associated with each disease. The risk variants were obtained from GWAS Catalog (<https://www.ebi.ac.uk/gwas/home> [↗](#)), during the period November 2021 to August 2022. The trait IDs used to retrieve data from GWAS Catalog for the different diseases were EFO_0000712 (Stroke), EFO_0001645 (IHD), EFO_0000537 (High SBP), MONDO_0005148 (T2D), MONDO_0005147 (T1D), EFO_0003884 (CKD), EFO_0007041 (High BMI) and EFO_0004611 (High LDL). The position of the risk variants in GRCh37 assembly was obtained, and variants less than 10000 bp apart were excluded using custom perl scripts. The total number of risk variants for each disease thus obtained are shown in table S8. The genotype of identified biallelic autosomal SNPs in unrelated individuals was extracted from the 1000 Genome VCF files (<https://www.internationalgenome.org/> [↗](#)). The proportion of ancestral populations in each individual was estimated from their genotype using a model-based clustering approach⁶¹. The admixture model with correlated allele frequencies was specified to cluster the individuals into either five clusters or three clusters (in case of BMI). The genotype was converted to eigenvectors using principal component analysis^{62,63}.

Shared and Unique risk variants among ethnicities

The number of GWAS risk variants for stroke shared among, as well as, unique to the five super-populations in 1000 Genomes (African, East Asian, South Asian, European and American) was obtained (**Fig. 6** [↗](#) and Table S6). A risk variant was considered to be present in a population if the alternate allele frequency in 1000 Genomes was greater than or equal to 0.05. For each GWAS risk loci, the gene(s) the variant maps to was obtained and shared genes among the populations was also estimated (table S6).

Calculation of Linkage Disequilibrium (LD) of risk variants of stroke in South Asia

Proxy variants ($R^2 > 0.01$) in the region ± 500 Kb of the risk variant of stroke present in South Asian population was obtained from LDlink⁶⁴. Among the proxy variants, variants with minor allele frequency (MAF) less than 0.1 were selected along with the risk variant as low frequency variants, and variants with MAF greater than 0.1 were termed as common variants. LD between two alleles A and B is quantified using the coefficient of linkage disequilibrium D_{AB} calculated using the equation $D_{AB} = p_{AB} - p_A p_B$, where p_i represents the frequency of the allele i or haplotype i . To be able to compare the level of LD between different pairs of alleles, D is normalized as follows: $D' = D / D_{max}$, where $D_{max} = \max\{-p_A p_B, -(1-p_A)(1-p_B)\}$ when $D < 0$ and $D_{max} = \min\{p_B(1-p_A), p_A(1-p_B)\}$ when $D > 0$ ⁶⁵. Estimates of D' were calculated separately for low frequency variants and common variants, and plotted using the R library *gaston*.

Data Availability

The datasets analysed during the current study are available in the GBD database, at <https://vizhub.healthdata.org/gbd-results/?params=gbd-api-2019-permalink/fe8b05e8222bcf3ec3af555762006f2a> [↗](#). All other materials including computer code will be available upon request. Please contact corresponding author for the same.

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Author contributions

RS, ASN and MB conceptualized and designed the workflow, and wrote the manuscript. RS performed the trend and statistical analyses, principal component analysis and population structure analysis, and generated figures and tables. ASN and MB provided overall guidance and direction.

Competing interests

The authors declare that they have no competing interests

Materials correspondence

The datasets analysed during the current study are available in the GBD database, at <https://vizhub.healthdata.org/gbd-results/?params=gbd-api-2019-permalink/fe8b05e8222bcf3ec3af555762006f2a> .

All other materials including computer code will be available upon request. Please contact corresponding author for the same.

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Editors

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Reviewer #1 (Public Review):

Summary:

The paper measures the prevalence and mortality of stroke and its comorbidities across
geographic regions in order to find differences in risks that may lead to more effective
guidance for these subpopulations. It also does a genetic analysis to look for variants that
may drive these phenotypic variations.

Strengths:

The data provided here will provide a foundation for a lot of future research into the causes
of the observed correlations as well as whether the observed differences in comorbidities
across regions have clinically relevant effects on risk management.

Weaknesses:

As with any cross-national analysis of rates, the data is vulnerable to differences in
classification and reporting across jurisdictions. Furthermore, given the increased death rate
from COVID-19 associated with many of these comorbid conditions and the long-term effects
of COVID-19 infection on vascular health, it is expected that many of the correlations
observed in this dataset will shift along with the shifting health of the underlying
populations.

<https://doi.org/10.7554/eLife.94088.1.sa1>

Reviewer #2 (Public Review):

Summary:

The authors have analyzed ethnogeographic differences in the comorbidity factors, such as diabetes and heart disease, for the incidences of stroke and whether it leads to mortality.

Strengths:

The idea is interesting and the data are compelling. The results are technically solid.

The authors identify specific genetic loci that increase the risk of a stroke and how they differ by region.

Weaknesses:

The presentation is not focused. It would be better to include p-values and focus presentation on the main effects of the dataset analysis.

<https://doi.org/10.7554/eLife.94088.1.sa0>