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Article:

Gillott, RG, Willan, K, Kain, K et al. (2017) South Asian ethnicity is associated with a lower prevalence of atrial fibrillation despite greater prevalence of established risk factors: a population-based study in Bradford Metropolitan District. EP Europace, 19 (3). pp. 356-363. ISSN: 1099-5129

<https://doi.org/10.1093/europace/euw010>

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South Asian ethnicity is associated with a lower prevalence of atrial fibrillation despite greater prevalence of established risk factors: a population based study in Bradford Metropolitan District.

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Abstract

Background

Previous studies indicate that South Asians (SA) may have a reduced risk of developing atrial fibrillation (AF) despite having a higher prevalence of traditional cardiovascular risk factors. This observational study was designed to explore the relative differences between SAs and Whites in a well-defined, multi-ethnic population with careful consideration of traditional cardiovascular risk factors that are thought to contribute to the development of AF.

Methods and Results

Anonymised data from 417,575 adults was sourced from primary care records within Bradford Metropolitan District, UK. AF diagnosis was indicated by presence on the AF QOF register. Self-reported ethnicity was mapped to census ethnic codes.

The age-standardised prevalence rates of AF were calculated for comparison between the White and SA populations; our study sample presented relative proportions of 2.39% and 0.4%. Multivariable logistic regression analysis was performed to estimate the odds of developing AF given SA ethnicity. Adjustment for age, sex and established risk factors found a 71% reduction in odds of AF in SAs when compared to Whites (OR: 0.29, 95% CI: 0.26–0.32). When stratified by ethnicity, analyses revealed significantly different odds of AF for patients with diabetes; diabetes was not associated with development of AF in the SA population (0.81; 95% CI: 0.63–1.05).

Conclusions

This study, in a multi-ethnic population, presents ethnicity as a predictor of AF where prevalence is significantly lower in SAs compared to Whites. This is despite SAs having a higher frequency of established risk factors for the development of AF, such as IHD, heart failure, hypertension and type 2 diabetes. These findings are consistent with previous literature and add weight to the need for further investigation, though this is the first study to investigate the differential associations of individual risk factors with development of AF.

Introduction

Atrial fibrillation (AF) affects 1-2% of the general population, and its prevalence is expected to double over the next 50 years (1). It is associated with a 4-5 times increase in stroke risk (2) and a 1.5-1.9 fold increased risk in mortality (3). Patients with AF also have reduced cardiac output which leads to heart failure; this results in an increased frequency of hospital admissions (1) and reduced quality of life.

The established major risk factors for developing AF are high blood pressure, coronary heart disease, heart failure, diabetes and age (1). Currently there are no effective strategies to prevent development and the mainstay of management is treatment of the condition once it manifests. The management of AF can be challenging (1).

Previous research finds a lower prevalence of AF in the South Asian (SA) population compared to White Europeans despite a higher prevalence of established risk factors such as diabetes and coronary artery disease (4) (5) (6) (7). Population characteristics are not well defined with regards to hypertension where some studies report that SAs have a higher prevalence and others report lower, although age is often overlooked (8) (9). Ethnicity in such research is not often well defined and samples may not be representative according to census data. If SAs have a lower prevalence of AF despite having higher traditional cardiovascular risk factors, understanding the reasons may have implications for primary preventative strategies.

Bradford metropolitan district (BMD) has an SA population of 26.83% (10) and the largest proportion of people of Pakistani ethnic origin (20.3%) (10). The predominant SA population of Bradford comprises individuals who immigrated to the UK from Mirpur district (Pakistan) in the 1950-1960s and their progeny (11). This unique setting allows a novel comparison of SAs (with common genealogy) and Whites, whilst minimising potential bias from confounding environmental factors.

This observational study was therefore designed to explore the association between SA ethnicity and development of AF in a well-defined multi-ethnic population with consideration of traditional cardiovascular risk factors.

Methods

Anonymised records of all adults (aged 18+) registered with a GP in BMD as of 01/07/2013 were sourced from the General Practice (GP) database, SystmOne, of all adult patients (aged 18+) registered as of 01/07/2013 with a GP in BMD. The district has an adult population of 385,873 and data from all 82 GPs in BMD was obtained.

The data export was undertaken by the West and South Yorkshire and Bassetlaw Commissioning Support Unit. The dataset contained demographic variables including age, sex and self-reported ethnicity, along with prescribed cardiovascular medication and whether the patient had been included on any of the following Quality Outcomes Framework (QOF) registries: AF, diabetes, heart failure, hypertension, peripheral arterial disease, ischemic heart disease or stroke.

Data preparation

Data were stored in a relational SQL database and scripts were written to 'clean' the dataset in preparation for analysis, generating the necessary derived variables.

Ethnicity values within the GP dataset were Read Coded. These codes provide a 'thesaurus of clinical terms' and are used to document patient findings and procedures in information technology systems throughout primary care in the UK. Values were mapped to the 18 national Ethnic Category codes, as used in the 2001 and 2011 census' (using previous studies as guidance), and are the accepted standard in the NHS Data Model and Dictionary for England Version 3. For the purposes of these analyses, we used the six higher-level categories: White, Mixed, Asian or Asian British, Black or Black British, Other Ethnic Group and Not stated. As the national codes do not differentiate between the Asian sub-regions we used the definition rendered by the United Nations (12) to determine those countries that are considered to be SA (see Supplementary file 1). Only those patients that were mapped to White or SA categories were used in the analysis.

The QOF registry data was cleaned to provide a binary data format; those records that were neither marked positively nor negatively were re-coded as negative. AF diagnosis was indicated by a patient being placed on the AF QOF register by their GP; these patients were assigned diagnostic Read Codes (v3) G5730% or G573.% in their electronic medical record. Atrial fibrillation resolved, coded

as Read Code v3 XaLFz, is excluded from the QOF dataset. Analysis was not possible in 6714 patients because of missing data in key QOF and/or medical history fields.

The study population was compared for proportional equivalence with the latest available census data (27/03/2011) for the BMD with regards to ethnicity and sex for each age category. We also explored the proportional change in ethnic representation between 2001 and 2011 based on the Census data for both Bradford and England and Wales.

Data for each of the risk factors (aged 65-74, aged ≥ 75 , diabetes, heart failure, ischaemic heart disease, peripheral arterial disease and hypertension) were also derived from the dataset.

Statistical methods

All analyses were conducted using the statistical package R (The R Project for Statistical Computing) (13).

Crude prevalence of AF in the study population was calculated using the complete adult (18+) general practice population. Direct standardization for age was conducted by matching to the 2011 Bradford Census (14).

The prevalence of AF and established risk factors were compared between the two ethnic subgroups using the two-proportion z-test. False discovery rate (FDR) correction for multiple testing was used. In order to acknowledge the variation in age distribution between these populations, data were also examined in three age groups.

In the first instance, multivariable logistic regression analysis was performed to estimate the odds of developing AF when South Asian compared with White. The complete regression model adjusted for age, sex, hypertension, heart failure, diabetes and ischemic heart disease. The minimum sufficient set of confounders was identified using a Directed Acyclic Graph (DAG) tool (15) with guidance from *a priori* clinical knowledge. The continuous variable age was discretised to reflect those categories considered to be of clinical relevance (<65, 65-74, ≥ 75); the remaining covariates were included dichotomously, denoting whether or not the diagnosis was present.

Data were then stratified by ethnicity and subgroup analyses were performed to investigate the differential odds of AF given each of the potential risk factors; separate multivariable logistic

regression models were fit to characterise the exposure-outcome relationships for each risk factor as directed by individual DAGs. A total of 14 models were run (Supplementary file 2); model fit was assessed by generation of ROC (Receiver Operating Characteristic) curves, with consideration of the area under the curve (AUC) values obtained. Odds ratios were estimated for the covariates previously mentioned and presented graphically as a forest plot to allow visual comparison between ethnicities.

Results

The dataset comprised a total of 417,575 individuals registered at BMD practices; this figure is 8% greater than the 2011 census population (385,873) (14) and 21.2% higher than the 2001 census (344,600) (16). A total of 6714 subjects were not considered for analysis due to incomplete data (Figure 1). The remaining GP records were classified into 177 distinct ethnicity Read Codes. Approximately 6.9% (28,715) of our population could not be resolved to an ethnic category; Read Codes present in the GP record were equivalent to 'not otherwise specified' or 'not stated'. Complete case analysis was conducted upon 277,218 cases, where only White (204,193) and South Asian (73,025) data were retained (Figure 1).

As the Census dataset does not strictly classify SA as a sub-set, distribution of the total Asian population from the 2011 Bradford Census was compared to these data in terms of ethnic category, sex and age. By proportion, our datasets were not significantly different for any sex/age/ethnicity combination; this validates our representation of the Bradford population.

The SA sample has a mean age approximately 10 years lower than that of the White population (White: 48.85 (SD:18.93), SA: 39.39 (SD:15.58)) (Figure 2). The age distribution in SAs is skewed (where the population is younger), compared with Whites.

For the entire population, we detected a 1.91% crude prevalence of AF (5304 cases). The total age adjusted prevalence was 2.39% and 0.4% for Whites and SAs respectively (Table 2). As the population distribution SAs and Whites is very different (Figure 2), we grouped individuals into three different age brackets; 50-65 (Table 1b), 65-79 (Table 1c) and 80+ (Table 1d). The prevalence of AF was lower in SAs compared to Whites despite the significantly higher prevalence of "traditional" risk factors for AF (i.e. hypertension, diabetes, coronary disease and heart failure) (Table 1b-d, Figure 3). Furthermore, when adjusted for age, sex, heart failure, hypertension, diabetes and ischemic heart disease, multivariable logistic regression analyses demonstrated a 71% reduction in odds of AF in SAs when compared to Whites (OR: 0.29, 95% CI: 0.26 –0.32). An AUC value of 0.91 was obtained for this model.

Further regression analyses determined the role of individual cardiovascular risk factors of AF within each ethnic group. In both cohorts, hypertension, heart failure, IHD and aging significantly increased the likelihood of developing AF. However, diabetes did not increase the odds of AF in the SA sample (0.81; 95% CI: 0.63-1.05), but did so in Whites (1.28; 95% CI: 1.19-1.38). Additionally, White females were less likely to have AF compared to SA females (Figure 4). The association between AF and co-morbid diabetes and hypertension was also explored to find that within the SA sample (n=121), the odds ratio for AF with diabetes and hypertension as a combined risk factor is 0.76 (CI: 0.57-1.01). In whites (n=944), the odds ratio was 1.45 (1.33-1.57). All models demonstrate good fit with a range of AUC values between 0.87 and 0.9.

Discussion

Bradford is the 4th largest metropolitan district in England and has a SA population of 26%. The majority of the SA population are of Pakistani ancestry (77%), with a large proportion originating from the small Mirpur District of South Azad Kashmir, Pakistan (11). This is the first study to investigate the prevalence of AF within distinct ethnic groups residing in a shared environment, where the majority of the SAs share similar genealogy. Comparisons are made between White and SA cohorts from a stable resident population with low mobility – the influence of environmental factors is therefore similar for both groups. Stratified regression modelling was used to explore the differential effects of ethnicity and define the association of cardiovascular risk factors with AF prevalence. Confidence intervals produced for all models using SA data are notably wider than those for White data and this is likely attributable to the difference in sample size; however this did not significantly detract from model fit.

The predominantly homogenous nature of the sample is advantageous where inclusion of any other SA population, such as those from the Indian subcontinent for example, brings complications due to the differential incidence of rheumatic mitral valve disease (17). Ethnicity data from this study is self-reported, which has been shown to be more accurate than when coding is completed by an

independent observer (18). These data are consistent with census population counts and importantly, the overall prevalence of AF in our cohort is in line with previous published data.

This dataset comprised 145 SA AF patients >75 years old and although this number is slightly smaller than analysed in previous literature (5), the difference is minimal. The ethnic origin of patients within this group was strictly defined prior to analysis and this, together with the homogeneity of the sample population, gives strength to the publication that other publications do not share.

A further strength is the use of QOF coded data for indication of the presence of AF and relevant comorbidities. As all GPs in Bradford use SystmOne, and data collection is incentivised under the QOF scheme, maximal data completion is encouraged. QOF data is considered to be one of the most reliable datasets immediately available as it is required to calculate payments as part of the GP contracts, hence there is financial incentive to ensure that data are collected and recorded accurately.

Using these data, obtained as part of routine healthcare, we add support to previous literature with demonstration of a significantly lower age-standardised prevalence of AF within the SA population when compared to Whites, despite having a higher proportion of cardiovascular disease, heart failure, diabetes and hypertension. This is the first study to examine the ethnic differences in aetiology rather than the resulting disease, and multivariable analyses translated this to a 71% reduction in odds of developing AF for SA patients. Ethnicity alone was identified to have a strong association with development of AF in adjusted analyses which demonstrated excellent predictive ability by AUC. In both groups, hypertension was found to have a strong association with AF. However, while White patients with diabetes have increased odds of AF, no association was found for SAs. It appears that the effect of hypertension is therefore somehow blunted in SAs, and this may be in association with diabetes. Explorative analyses found a paradoxical relationship between the combination of hypertension and diabetes in SA compared to Whites, in that while statistically non-significant, the odds for AF reduce for patients with both risk factors in SAs but not in Whites. Could

this be because in SAs, diabetes as a precursor for hypertension has a different pathophysiological mechanism to hypertension on its own?

We cannot conclude that diabetes and comorbid diabetes and hypertension have a differential mechanism in the development of AF without further evidence to validate this finding. No data are currently available to determine why, where established risk factors are more prevalent in SAs, the prevalence of AF is lower. There are a number of potential underlying mechanisms that may explain this, however. For example, there may be morphological differences between the White and SA heart.

There is evidence to suggest that the SA left atrium is smaller than the White atrium and this appears to be associated with a smaller body surface (19). A smaller LA may explain this discrepancy where early evidence from animal experiments showed that smaller mammals do not sustain AF because their atria do not have critical mass to allow the arrhythmia to perpetuate (20). This has also been demonstrated more recently by Allesie et al (21). Whilst this theory is interesting, conditions such as heart failure and hypertension would increase left ventricular end diastolic pressure and raise left atrial pressure causing atrial stretching and expansion. The SA atrium may be more resistant to this effect, or the process may take longer in SAs as the atrium is smaller. More recent data from animal studies negates the size hypothesis as the administration of sympathetic agents appears to nullify this effect (22). Therefore mechanisms beyond size could be responsible. The allometric scaling model may help to explain how size could affect function. Studies on the hearts of a number of mammals have suggested that the PR interval is directionally proportional to body mass (23). Moreover, data from studies on ventricular fibrillation models appear to support the notion that fibrillation cycle length is directly proportional to body mass to the power of $\frac{1}{4}$ (20). Theoretically, this non-linear relationship could translate to different AF cycle lengths in Whites versus SA and lead to differing susceptibilities. Part of the difference could be secondary to events at the ion channel level. There are reports of sodium channel variants in different ethnic groups which could either be protective or make patients more vulnerable to heart rhythm disorders (24). This mechanism is intriguing, but requires further work (20). Finally, the extracellular matrix composition may also be

different, or the response to fibrosis may be reduced in SAs. Work from our group has demonstrated a difference in matrix metalloproteinases in different ethnic groups (25). In addition, variants of the angiotensin II type 1 receptor in SAs appear to protect from non-alcoholic fatty liver disease in SA (26). It is possible therefore, that the difference in AF susceptibility is attributable to a different genetic makeup. Recently a number of genes have been identified and ethnic associations made (27) (28) (29). However, there is little information regarding the genetic profiles of SAs (30). An inherited protective effect may explain this difference, which could render the SA atria morphologically and physiologically different to that of the White population and potentially explain why this effect is evident in many reports (29).

Limitations

Although we feel that the sample is representative, there are a number of limitations. The prevalence of AF was derived from the QOF records provided by GP surgeries alone; we have not validated these diagnoses by scrutiny of ECGs and this may be a source of error. Further, if a QOF code for clinical diagnosis was not present in the record, we have assumed that the patient is free from disease. This approach neglects to consider those patients that have AF though have not had cardiac rhythm assessment to confirm diagnosis, and also basic errors during data entry – these points are true for both subgroups however, and are unlikely to introduce substantial bias.

Continuous variables such as blood pressure and BMI were collected in the original dataset, however as large amounts of data were poorly recorded or missing, these were unsuitable for inclusion in analyses; residual confounding may therefore remain and is a limitation of this work.

Additionally, we were unable to include unregistered individuals in analyses as data were unavailable and although we would expect this to be a small minority of the population, it should be considered a potential source of bias. Similarly, although the age, sex and ethnicity breakdown was comparable to census data overall, a group of individuals were excluded as their ethnicity was not coded; these patients may collectively represent a unique subset. However, despite these flaws, it is unlikely that a significant number of individuals have been omitted.

These analyses do not account for the potential difference in GP attendance rate by population subgroup and this may represent failure to address bias, though as all patients reside in the same area and therefore have the same access to healthcare, it is likely that all patients would present if symptomatic. It is acknowledged that many cases of AF are undiagnosed, though this is not expected to vary by ethnicity in this sample.

Further work

Further studies with larger sample sizes in subsets such as that of AF patients with comorbid hypertension and diabetes are required to validate the paradoxical reduction in odds for SAs.

Genetic studies for identification of potential genes that may protect from AF will be important to allow the difference in prevalence to be explained. Work also needs to be directed to address the concept of anatomical differences between the ethnic groups with imaging. Electrophysiological studies should be directed towards assessment of atrial conduction, refractoriness, atrial size and vulnerability to scarring.

Conclusion

This multi-ethnic, population-based study shows that the prevalence of AF is significantly lower in SAs compared to Whites. This is despite a higher frequency of IHD, type 2 diabetes, heart failure and hypertension in the SA population. The total AF prevalence in our cohort is similar to population estimates and findings from previous studies; this is important as it validates data sampling, and has not been properly accounted for in previous reports. These findings are consistent with previous papers and add weight to the need for further investigation with demonstration of differential odds of individual risk factors between ethnic subgroups.

Figure 1: Flow chart summarising study population & ethnic mapping from the total adult population

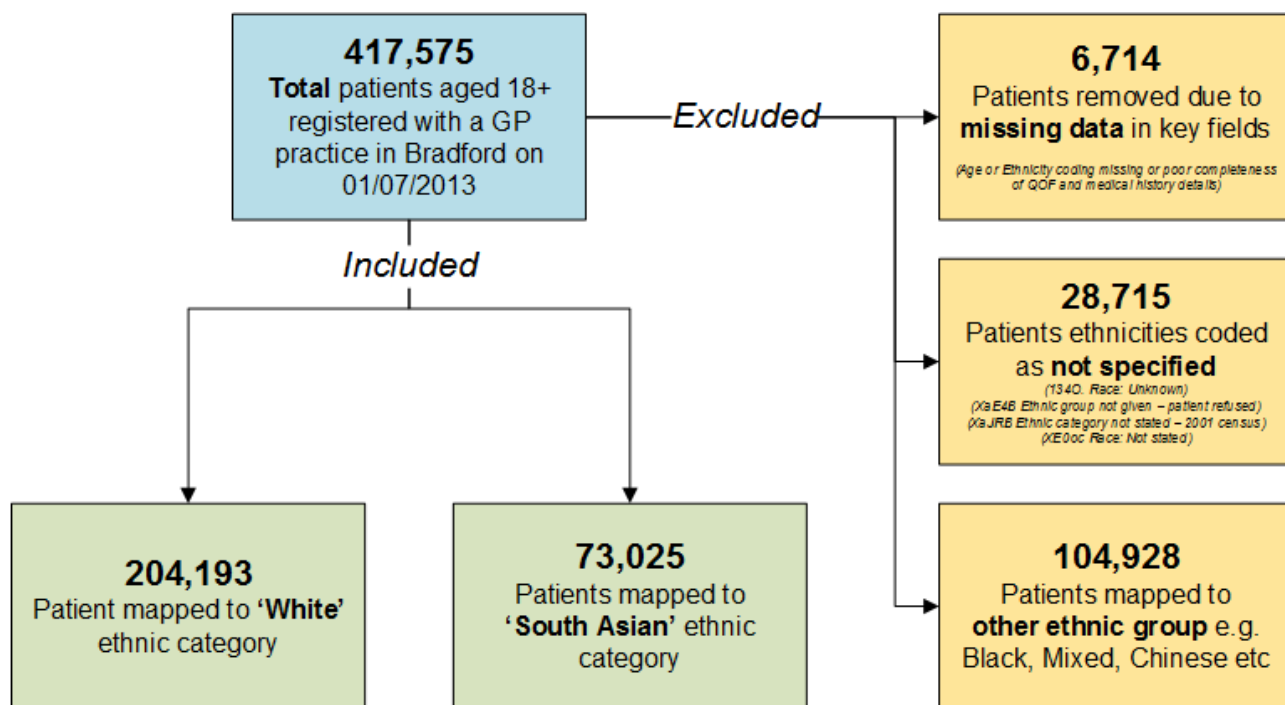


Figure 2: Population pyramid depicting the age distribution of the study population in ethnic sub-groups.

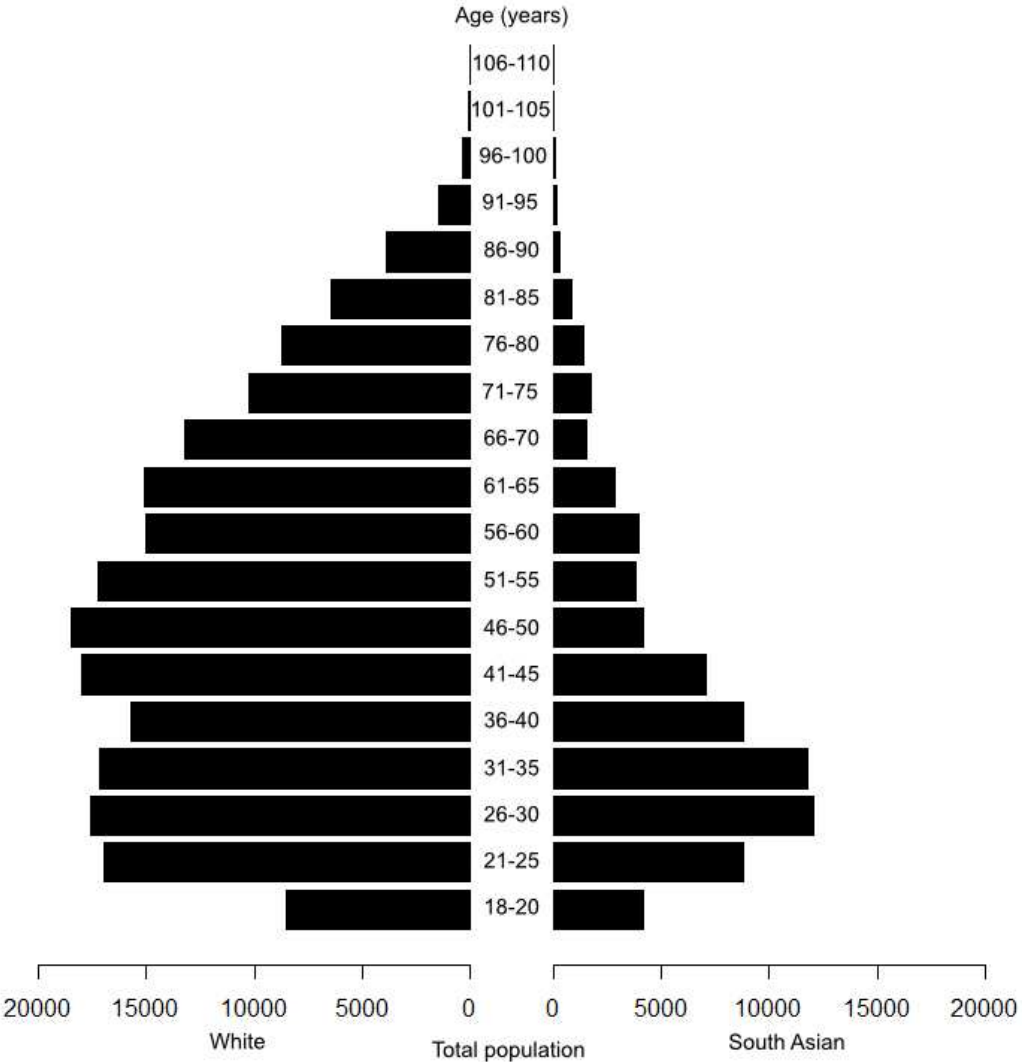


Figure 3: Age adjusted prevalence of AF in SAs and Whites

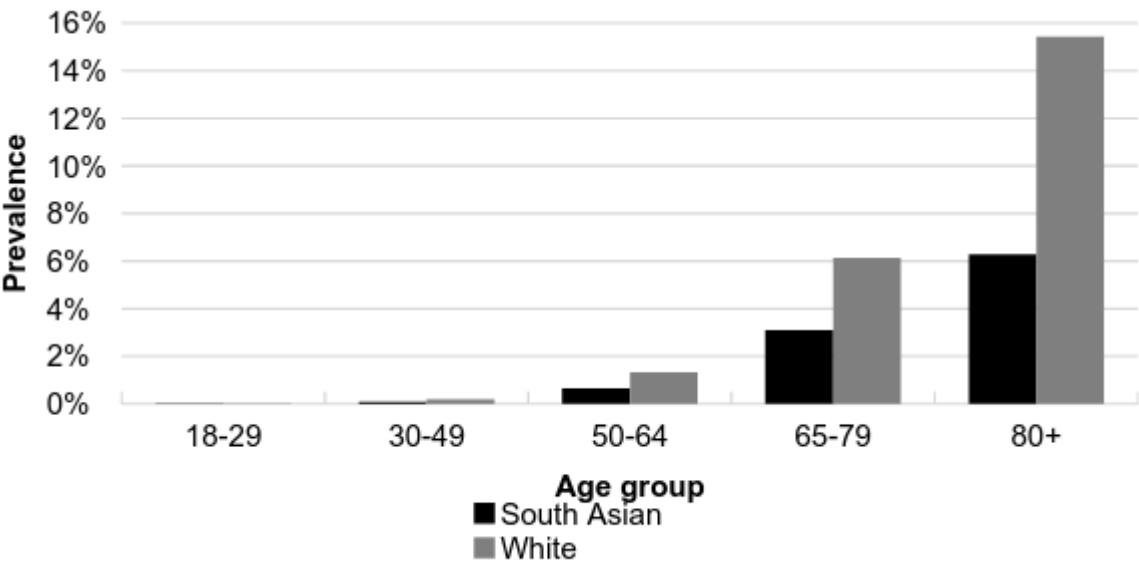


Figure 4: Adjusted odds ratios and 95% confidence intervals for each traditional risk factor following stratification by ethnicity for direct comparison. Estimates are adjusted for the minimum sufficient set of confounders deemed appropriate to estimate the direct effect within each exposure-outcome relationship (Appendix 2). W, White; SA, South Asian; PAD, peripheral arterial disease; IHD, ischaemic heart disease; 65-74 and >74 refer to age groups.

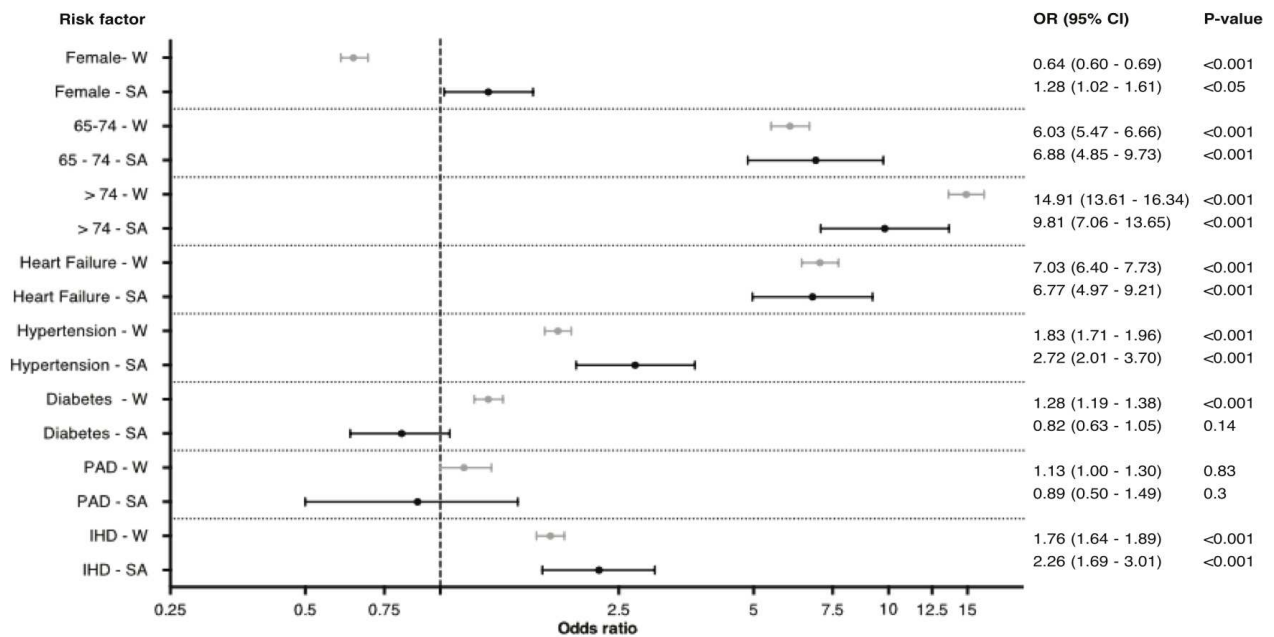


Table 1a: Whole population unadjusted for age

	Total population (277218)				
	White (n=204193)	%	South Asian (n=73025)	%	P-values *
Male : Female	95483 : 108710	46.76 : 53.24	37594 : 35431	51.48 : 48.52	
Age (mean, SD)	48.85 (18.93)	-	39.39 (15.58)	-	
AF	4968	2.43	336	0.46	<0.001
Heart failure	2658	1.30	551	0.75	<0.001
Hypertension	41278	20.22	9994	13.69	<0.001
Diabetes	15827	7.75	10025	13.73	<0.001
Peripheral arterial disease	3060	1.50	586	0.80	<0.001
Ischemic heart disease	12275	6.01	3034	4.15	<0.001
Stroke	6157	3.02	1017	1.39	<0.001

Table 1b: Individuals aged 50-64

	Total population (58617)				
	White (n=47774)	%	South Asian (n=10843)	%	
Male : Female	23344 : 24430	48.86 : 51.14	5510 : 5333	50.82 : 49.18	
AF	639	1.34	70	0.65	<0.00 1
Heart failure	331	0.69	135	1.25	<0.00 1
Hypertension	12088	25.30	4196	38.70	<0.00 1
Diabetes	4771	9.99	4213	38.85	<0.00 1
Peripheral arterial disease	609	1.27	225	2.08	<0.00 1
Ischemic heart disease	2622	5.49	1175	10.84	<0.00 1
Stroke	1097	2.30	352	3.25	<0.00 1

Table 1c: Individuals aged 65-79

	Total population (38793)				
	White (n=34095)	%	South Asian (n=4698)	%	
Male : Female	16223 : 17872	47.58 : 52.42	2115 : 2583	45.02 : 54.98	
AF	2092	6.14	146	3.11	<0.00 1
Heart failure	1023	3.00	233	4.96	<0.00 1
Hypertension	16907	49.59	2910	61.94	<0.00 1
Diabetes	6321	18.54	2450	52.15	<0.00 1
Peripheral arterial disease	1448	4.25	215	4.58	0.338
Ischemic heart disease	5414	15.88	1175	25.01	<0.00 1
Stroke	2583	7.58	392	8.34	0.083

Table 1d: Individuals aged 80+

	Total population (14914)				
	White (n=13559)	%	South Asian (n=1355)	%	
Male : Female	4844 : 8715	35.73 : 64.27	634: 721	46.79 : 53.21	
AF	2091	15.42	85	6.27	<0.00 1
Heart failure	1228	9.06	154	11.37	0.008
Hypertension	8663	63.89	862	63.62	0.896
Diabetes	2701	19.92	652	48.12	<0.00 1
Peripheral arterial disease	881	6.50	72	5.31	0.118
Ischemic heart disease	3825	28.21	380	28.04	0.922
Stroke	2226	16.42	186	13.73	0.129

Statistical significance estimated by two proportion z-test, * p-values adjusted for multiple testing using FDR; *** = $p < 0.001$

Table 2: Age adjusted prevalence of AF by ethnicity

	White			South Asian			Significance
	N	Cases of AF	Age adj. prev (%)	N	Cases	Age adj. prev (%)	
18-29	39,594	8	0	22,478	7	0.01	0.56
30-49	69,176	138	0.07	33,653	28	0.04	***
50-64	47,775	639	0.34	10,843	70	0.09	***
65-79	34,096	2,092	0.96	4,698	146	0.17	***
80+	13,559	2,091	1.02	1,355	85	0.08	***
Total	204,200	4,968	2.390	73,027	336	0.4	***

Statistical significance estimated by two proportion z-test, *** = $p < 0.001$

Acknowledgements

Theresa Munyombwe, Cardiovascular and Diabetes Research, Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM), University of Leeds, Leeds, United Kingdom.

Funding

Boehringer Ingelheim have partially funded this project

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Disclosures

Muzahir H Tayebjee has received a research grant for this study from Boehringer Ingelheim.

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M U Sivananthan	Co-author, manuscript advice
M H Tayebjee	Senior author, protocol and manuscript preparation

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