

## **Evidence for reduced susceptibility to cardiac bradyarrhythmias in South Asians compared with Caucasians**

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## **ABSTRACT**

### **Objectives**

To investigate ethnic differences in susceptibility to bradyarrhythmias in south Asian and white European patients in the UK by determining rates of permanent pacemaker (PPM) implantation for sinus node disease (SND) and atrio-ventricular block (AVB) in each ethnic group.

### **Methods**

We carried out a retrospective cohort study into new PPM implantation during the period 01 May 2006 - 31 March 2014, in patients of South Asian and Caucasian ethnicity resident in Leicestershire, UK. Numbers of individuals at risk in each ethnic group were derived from UK National Census data of 2011. Crude, and age-standardized incidence rates and risk ratios per thousand population of PPM implantation were calculated for Caucasians and South Asians.

### **Results**

During the study period, 4883 individuals from the Leicestershire population of 980,328 underwent PPM implantation, a cumulative implantation rate of 4.98/1000 population. The population cumulative PPM implantation rate for SND was 1.74/1000, AVB 2.83/1000, and other indications 0.38/1000 population. The crude incidence in Caucasians (6.15/1000 population) was higher than in South Asians (1.07/1000 population) and remained higher after age-standardization (5.60/1000 versus 2.03/1000,  $p < 0.001$ ). The age-standardized cumulative PPM implantation rates were lower in South Asians for both SND (0.53/1000 in South Asians; 1.97/1000 in Caucasians,  $p < 0.001$ ) and AVB (1.30/1000 in South Asians; 3.17/1000 in Caucasians,  $p < 0.001$ ). Standardized risk ratios (95% confidence interval) for PPM implantation in South Asians compared to Caucasians for all pacing indications, SND and AVB were 0.36 (0.36-0.37), 0.27 (0.27-0.28), and 0.41 (0.41-0.42) respectively.

### **Conclusions**

Rates of PPM implantation are lower in South Asians residing in the UK, compared to Caucasians. This observation raises the possibility of lower inherent susceptibility to bradyarrhythmias in South Asians compared to Caucasians. Studies aimed at identifying underlying mechanisms, including possible genetic differences, are warranted.

**Key words:** Pacemaker; ethnicity; sinus node disease; atrioventricular block; direct standardization.

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What is already known about this subject?

Many manifestations of cardiovascular disease show differences among ethnic groups. This is true for hypertension, coronary artery disease and heart failure. It is not known if ethnic differences exist in risk of bradyarrhythmia necessitating permanent pacemaker (PPM) implantation.

What does this study add?

In Leicestershire, an area of the UK with higher than average South Asian ethnic minority population, age-standardized risk of PPM implantation in South Asians were much lower compared to Caucasians for all pacing indications. In the context of higher cardiovascular disease risk factors and disease incidence, factors which might be expected to lead to increased risk of bradyarrhythmia and PPM implantation, our observations suggest the existence of ethnic variation in susceptibility to clinically important cardiac conduction disturbances.

How might this impact on clinical practice?

Ethnic differences in susceptibility to cardiac conduction abnormalities may have important implications for provision of appropriate secondary care cardiac services in areas with diverse ethnic populations. Genetic differences among ethnic groups might contribute to this phenomenon.

## INTRODUCTION

Ethnic differences exist with respect to several cardiovascular diseases. For example, compared to Caucasians, people of South Asian ethnicity (India, Pakistan, Bangladesh, Sri Lanka) have increased incidence of coronary artery and cerebrovascular disease (1-7). People of Afro-Caribbean / African ethnicity in the United Kingdom have higher incidence of cerebrovascular, peripheral vascular, and chronic kidney diseases, with lower rates of coronary artery disease (3, 4), while in North America African Americans have higher rates of cardiovascular disease compared to people of White ethnic background (8). People of East Asian ethnic origin (China, Japan, Korea, Taiwan) have lower coronary artery disease, and higher cerebrovascular disease, rates (8, 9). Possible contributory factors to these ethnic variations in cardiovascular diseases include differences in profiles of cardiovascular risk factors (1, 5, 10) or socio-economic conditions between ethnic groups (11-13), and differences in genetic susceptibility (7, 12, 13).

Bradyarrhythmias due to either sinus node disease (SND) or atrioventricular block (AVB) are an important cause of age-related cardiovascular morbidity. Presentation is typically with symptoms of dizziness, syncope or effort intolerance and either an abnormal resting ECG or rhythm monitoring can help to establish the diagnosis. While PPM implantation for all degrees of heart block may have symptomatic benefit, implantation in the context of Mobitz II, other higher degree AVB, and third degree heart block, has survival benefit (14, 15). On this background, European (14) and American (15) guideline indicate that PPM devices should be implanted for lower degree AVB and SND only if symptomatic. On this basis, the number of new PPM implants should equate closely to the incidence of clinically significant SND and AVB. Few studies have explored whether there are ethnic differences in the risk of bradyarrhythmias. Recent data derived from two combined large, prospective cohort studies in the USA suggested ethnicity as a risk factor of SND with a lower risk in African Americans compared to Caucasians (16). PPM implantation rates following admission with complete heart block have also been reported to be lower in African-Americans compared to Caucasians, differences which were only partly explained by ethnic variation in access to health insurance cover (17). Whether other ethnic groups have different risk profiles for SND or AVB compared to Caucasians remains unknown.

Individuals of South Asian ethnic origin make up the largest minority ethnic group in the United Kingdom (UK), constituting approximately 4.9 % of the total population (18). In the county of Leicestershire, individuals of South Asian ethnicity constitute approximately 15% of the population. We have reported higher incidence rates of coronary artery disease (19) and heart failure (20, 21) in the Leicestershire South Asian population compared to Caucasian patients, but similar (19, 20) or better (21) case-fatality. In this study, we aimed to use this enriched population with a high density of individuals of South Asian ethnicity to determine whether risk of bradyarrhythmias differ between South Asians and Caucasians by comparing

PPM implantation rates in these two ethnic groups. To evaluate whether any differences observed were site specific, we compared the indication (SND or AVB) by ethnic group.

## **METHODS**

**Study design and population:** We carried out a retrospective cohort study into cumulative PPM implantation rates at the University Hospitals of Leicester (UHL) between May 1<sup>st</sup> 2006 and March 31<sup>st</sup> 2014.

The population at risk (the exposed population) was the population of Leicestershire. Data regarding the population at risk were obtained from the UK National Census of 2011, obtained via the Office for National Statistics. The 2011 Census was carried out at the midpoint of our study period and was thus likely to provide an accurate assessment of the size of the population and the ethnicity profile as this information is mandatorily collected as part of the census. There was no large-scale migration of individuals into or out of the county during this period.

The study population constituted patients of Caucasian or South Asian ethnicity undergoing a PPM implantation at UHL, the primary provider of tertiary cardiology services to the people of Leicestershire. Ethnicity is routinely recorded locally for all procedures. Given small numbers of patients, and of PPM implantations, in other ethnic groups (Afro-Caribbean, other Africans, East Asians, Arabs, and others), these were not considered in this analysis. We excluded patients with previous PPM implantation who attended for a generator change or lead repositioning or replacement. Patients with PPM who attended for device upgrades were also excluded as were those whose indication for PPM implantation was AV node ablation for refractory atrial arrhythmias. Only patients undergoing new PPM implantation for bradyarrhythmia were retained for the study. The UK total population from the 2011 census was used as the population for direct standardization.

Case ascertainment was achieved through the department of cardiology database which is fully complete, up to date, and regularly audited. For each PPM implanted, the indication of SND or AVB was recorded, based on the indication recorded by the implanting physician. Our institution is the only NHS health care facility in the county of Leicestershire at which PPM implantation takes place. This study was conducted as part of a clinical audit and therefore did not require Ethics Committee approval.

**Statistical analysis:** Crude and age-specific cumulative PPM implantation rates per thousand population were calculated for Caucasians and South Asians. Each patient was categorised in to one of four age groups; < 25 years, 25-49 years, 50-74 years, and ≥ 75 years. Attempts to categorize into smaller age bands were hampered by small numbers, or the absence of implantation events in some age bands. In calculating the incidence, the numerator consisted of PPM first implants for each ethnic group, in total and by age group, while the denominator

was the respective population from the 2011 census. In view of differences in age structure of the Caucasian and South Asian populations (Caucasians were on average older), PPM implantation rates were directly standardised using the UK general population from the 2011 census. Age-specific crude PPM implantation rates for each ethnic group were applied within each age group (< 25 years, 25-49 years, 50-74 years, and  $\geq$  75 years) of the total UK population to obtain the age-specific expected event rates. The total number of expected, age-standardized events for each ethnic group was obtained by summing the age-specific events. We then calculated the age-adjusted incidence per 1000 population. Crude and age-standardized risk ratios of PPM implantation for Caucasians compared to South Asians were calculated. Subgroup analyses for SND and AVB were also carried out. Analysis were performed using STATA 11.

## RESULTS

### Patient characteristics

In the 2011 Census, the Leicestershire population of 980,328 contained 761,403 (77.7%) individuals of Caucasian, 155,500 (15.8%) of South Asian, and 63,425 (6.5%) of other ethnicity respectively. During the study period, a total of 4883 patients received a first PPM for bradycardia at UHL. After exclusion of individuals from other minority ethnic groups (n=37), a total of 4846 patients with first implants were retained in the analysis, of which 4679 (96.55%) were Caucasians and 167 (3.45%) were South Asians (Figure 1).

The demographic characteristics of patients who underwent PPM implantation, stratified by Caucasian/South Asian ethnicity are shown in Table 1. Caucasians were older and had a higher rate of atrial arrhythmias compared to South Asians. There were no significant differences overall in the main presenting symptoms and indications of PPM implantation between Caucasians and South Asians. However, South Asians were more likely than Caucasians to require pacemaker implantation in the context of an urgent presentation (Table 1).

### Cumulative incidence of permanent pacemaker implantation by ethnicity, age and indication

The cumulative PPM implantation incidence for the total population during the study period was 4.98/1000 inhabitants. The incidence of PPM implantation for SND was 1.74/1000 inhabitants, AVB 2.83/1000 inhabitants, and other indications 0.38/1000 inhabitants. These indications were not mutually exclusive.

Cumulative total PPM implantation incidence as well as those for the two main indications (SND and AVB) stratified by ethnicity and age groups are shown in **Table 2**. In both Caucasians

and South Asians there were proportionately more implants for AVB than for SND and rates of implantation increased dramatically after the age of 75 years. The unadjusted cumulative total PPM implantation rate in Caucasians (6.15/1000 population) was higher than in South Asians (1.07/1000), as were the incidence rates individually for AVB and SND (**Table 2**).

Because of the differences in the age structure of the Caucasian and South Asian populations (**Table 2**), with the South Asian being substantially younger, we computed age-specific and total incidence rates for a whole UK population based on 2011 Census data using the rates observed in the two ethnic groups (**Table 3**). This gave age-standardised cumulative total PPM implantation rates of 5.60/1000 in Caucasians and 2.03/1000 in South Asians. The age-standardized incidence rates of PPM implantation for SND was 1.97/1000 in Caucasians compared to 0.53/1000 in South Asians, while corresponding, age-standardized rates for AVB were 3.17/1000 and 1.30/1000 respectively (**Table 3**).

### **Incidence risk ratios**

The crude and age-standardized risk ratios (RR) of PPM implantation in South Asians compared to Caucasians are shown in **Table 4**. Comparing South Asians to Caucasians, the standardised RR was lower at 0.36 (95% CI 0.36-0.37) i.e. the standardised RR was higher for Caucasians at 2.70 (95% CI 2.68-2.71) compared to South Asians. Similar patterns were evident for PPM implantation for the indications of SND and AVB.

In view of small numbers of events in patients in younger age categories, by way of sensitivity analysis, we calculated RR for patients aged  $\geq 50$  years of age. As can be seen in Table 4, the age-standardised RR for PPM implantation was lower in South Asian patients for all indications, for sinus node dysfunction and for atrioventricular block (0.38, 0.28 and 0.43 respectively, all  $p < 0.0001$ ).

## **DISCUSSION**

To the best of our knowledge, this is the first study to report differences in PPM implantation rates between Caucasians and South Asians. We observed an age-standardised first PPM implantation rate which was 2.7 times higher in Caucasian, compared to South Asian patients. This difference was apparent in implantation rates for both sinus nodes disease and atrioventricular block. As rates of PPM implantation are likely to be good surrogate for rates of clinically significant bradyarrhythmias, our data suggest that these conditions are much less common in South Asian patients in the UK, compared to the Caucasian population.

Individuals of South Asian origin constitute the single largest ethnic minority group in the UK, approximately 5% of the population (18). In Leicestershire, South Asians constitute a much higher proportion of the population, 15.8% based upon 2011 Census figures. In this context, the Leicestershire population is one in which ethnic differences in the epidemiology of individual disease states can be assessed with greater robustness than is possible in other areas. In this setting, our data indicating lower rates of PPM implantation in South Asian patients are likely to be reliable.

It has been reported that African American men are less likely to be hospitalised for SND than white men (22). A recent publication using combined data from two large prospective cohort studies in the USA suggested ethnic differences in the risk of sick sinus syndrome, with African Americans having a 41% relative risk reduction compared to whites (16). On this background, our observations support the notion of higher risk of cardiac bradyarrhythmias in Caucasians compared to other ethnic groups.

There are a number of possible explanations for our observations. First, ascertainment bias, leading to under-diagnosis of cases of bradyarrhythmia in South Asian patients, either through poor access to, or underuse of, health services. Factors contributing to poor health access in ethnic minorities include linguistic barriers, level of literacy, and cultural beliefs (23). Data from the USA suggest socioeconomic status can contribute, to some extent, to differences in rates of PPM implantation in African Americans and other ethnic minority groups compared to Caucasians (26). Some reports have suggested underutilization of healthcare services by people of lower socioeconomic class and the elderly in a UK setting (24) while others have not identified such an association (25). We did not have access to details of socioeconomic status in the patients in our population. However, in the UK access to health care services is equitable, and health seeking behaviours similar, in South Asians compared to Caucasians (24, 25). Indeed we have reported previously that South Asian patients with heart failure appear to access hospital services at an earlier stage of disease (21) and more frequently (20) than white patients in our population.

It may be argued that socioeconomic and cultural differences might influence differences in cardiovascular disease risk between ethnic groups. Cardiovascular disease incidence rates are higher in South Asians in our locality compared to Whites (19). Further, cardiovascular disease risk factors are more prevalent in South Asians compared to White patients, with the exception of smoking (19, 20, 21). It is unlikely that higher prevalence of cardiovascular disease risk factors together with equity of health-care access would result in lower rates of bradyarrhythmia and PPM implantation observed here.

Second, there could be a problem of under-treatment, or differential implantation of PPM, by clinicians influenced by the ethnic origin of the patient. This is unlikely, with studies utilising data from U.K. national registries indicating equitable provision of medical treatment and



procedures for cardiovascular diseases for South Asians and White Europeans in the UK (5, 26).

Third, as with other cardiovascular diseases, biological differences may underpin the variation among ethnic groups in terms of the propensity to sinus node dysfunction and atrioventricular block. Specifically, recent genome-wide association studies have identified genetic variants that are associated with risk of sick sinus syndrome (27) and parameters of atrio-ventricular cardiac conduction (28). Further, some reports have suggested ethnic differences in single nucleotide polymorphisms associated with cardiac QRS duration and PR interval (29). While we are not aware of demonstration of such differences specifically between South Asian and White European populations, it is possible that the presence of ethnic-specific variants contribute to the relative protection of South Asians from bradyarrhythmias. Interestingly, the incidence and prevalence of atrial fibrillation (AF) has also been reported to be higher in Caucasians when compared to other ethnic groups, even when ascertainment bias has been overcome, suggesting lower susceptibility to AF in non-White ethnic groups (30). Indeed we observed lower AF prevalence in South Asians in this report and previously in patients hospitalised with heart failure (21). Whether the same mechanisms are responsible for the lower incidence of both bradyarrhythmias and AF in South Asians remains to be determined. Elucidation of these mechanisms may provide novel clues to the development of novel, non-device based treatments for these disorders.

## **LIMITATIONS**

Our data from a single centre may not be generalizable to South Asian patients in other areas of the UK. However significant variance from our observations are unlikely, given the uniform provision of National Health Service provision across the country. We were unable to explore PPM implantation rates in ethnic minority groups other than South Asian, in view of very small numbers in our population. We are unable to discount ethnic differences in seeking and accessing health care health, particularly among elderly South Asian individuals. However, as already noted, our local South Asian population appears to access health care in a similar way to other groups; moreover our data showed that the difference in implant rates was apparent across all age strata. With the use of census data and age-standardization statistical methods, it was not possible to correct for other possible confounding risk factors for bradyarrhythmia. However as noted above, these covariates, with the exception of smoking, are more prevalent in South Asians, and cardiovascular disease rates are higher and we would have expected a higher rate of PPM implantation in South Asians, rather than the lower rates observed. With regard to case ascertainment, we acknowledge we may have failed to identify residents undergoing PPM implantation while outside of our area. Such numbers are likely to be very small and unlikely to have influenced our observations. Finally, although the incidence of PPM implantation is

likely to reflect the incidence of clinically significant SND and AVND, this is a surrogate for the true incidence of SND or AVND. Our study did not identify asymptomatic SND and lower degree AVN disease. Finally, we recognise residual confounding remains a possibility, as the main results of this study were only age-standardized.

## **CONCLUSIONS**

The rate of permanent pacemaker implantation is lower in South Asians residing in the UK, compared to Caucasians. In the setting of equitable access to health care, our observations raise the possibility of lower, potentially genetic, susceptibility to bradyarrhythmias in South Asians. Future studies aimed at identifying any underlying driving genetic markers are warranted.

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## **Conflicts of Interest**

None of the authors has any conflict of interest relevant to this study

**Table 1: Characteristics of patients undergoing permanent pacemaker implantation by ethnicity.**

		<b>Caucasians</b>	<b>South Asians</b>	<b>P value</b>
<i>Number</i>		4679 (96.55%)	167 (3.45%)	
Age (mean (SD))		75.12 (14.32)	70.45 (14.90)	<0.001
Gender (male)		2819 (60.26%)	96 (57.49%)	0.472
Presence of symptoms		3832 (81.95%)	141 (84.43%)	
	Syncope	1811(38.73%)	61 (36.53%)	
	Presyncope	1668(35.67%)	57 (34.13%)	0.412
	Dyspnoea	515 (11.01%)	27 (16.17%)	
AF/Atrial flutter		903 (19.30%)	12 (7.19%)	<0.001
Indication	SND	1648 (35.22%)	48 (28.74%)	
	AVB	2655 (56.74%)	103 (61.68%)	0.268
	Other	353 (7.54%)	12 (7.19%)	
	Unknown	63 (1.35%)	4 (2.40%)	
Dual chamber PPM		2646 (56.65%)	107 (64.07%)	0.057
Urgency	Elective	2359 (50.42%)	68 (40.72%)	
	Urgent	2272 (48.56%)	95 (56.01%)	0.017
	Emergency	48 (1.03)	4 (2.40%)	

SND = Sinus node dysfunction; AVB = Atrioventricular block; 40 patients had both SND and AVB; AF = Atrial fibrillation; SD = Standard deviation. Symptoms were predominantly presyncope, syncope, dyspnoea, and to a lesser extent palpitations and chest pain.

**Table 2: Crude cumulative incidence rates of permanent pacemaker implantation in Leicestershire May 2006 to March 2014 for all indications (Table 2A), sinus node dysfunction (Table 2B) & atrioventricular block (Table 2C).**

**Table 2A: Crude cumulative incidence rates for all indications**

Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Caucasian population in Leicestershire census 2011	Number of PPM	Incidence of PPM implantation	Asian population in Leicestershire census 2011	Number of PPM	Incidence rate of PPM implantation
< 25 years	226231	86	0.38 ‰	58116	4	0.07 ‰
25-49 years	248517	132	0.53 ‰	59837	6	0.10 ‰
50-74 years	220471	1509	6.84 ‰	33002	79	2.30 ‰
≥ 75 years	66184	2952	44.60 ‰	4545	78	17.16 ‰
Total	761403	4679	6.15 ‰	155500	167	1.07 ‰

**Table 2B: Crude cumulative incidence rates for sinus node dysfunction (SND)**

Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Caucasian population in Leicestershire census 2011	Number of PPM	Incidence rate of PPM implantation	Asian population in Leicestershire census 2011	Number of PPM	Incidence rate of PPM implantation
< 25 years	226231	21	0.09 ‰	58116	1	0.02 ‰
25-49 years	248517	58	0.23 ‰	59837	2	0.03 ‰
50-74 years	220471	579	2.63 ‰	33002	28	0.85 ‰
≥ 75 years	66184	990	14.96 ‰	4545	17	3.74 ‰
Total	761403	1648	2.16 ‰	155500	48	0.31 ‰

**Table 2C: Crude incidence rates for atrioventricular block (AVB)**

Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Caucasian population in Leicestershire census 2011	Number of PPM	Incidence rate of PPM implantation	Asian population in Leicestershire census 2011	Number of PPM	Incidence rate of PPM implantation
< 25 years	226231	59	0.26 ‰	58116	3	0.05 ‰
25-49 years	248517	63	0.25 ‰	59837	3	0.05 ‰
50-74 years	220471	776	3.52 ‰	33002	44	1.33 ‰
≥ 75 years	66184	1757	26.55 ‰	4545	53	11.66 ‰
Total	761403	2655	3.49 ‰	155500	103	0.66 ‰

PPM=Permanent Pacemaker; ‰=per thousand

**Table 3: Age-standardized rates of permanent pacemaker implantation in Leicestershire May 2006 to March 2014 for all indications (Table 3A), sinus node dysfunction (Table 3B) & atrioventricular block (Table 3C).**

**Table 3A: Direct standardization cumulative incidence rates for all indications**

Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Standard UK population Census 2011	Age-specific PPM incidence rates	Expected number of PPM cases in standard UK population	Standard UK population Census 2011	Age-specific PPM incidence rates	Expected number of PPM cases in standard UK population
< 25 years	19395000	0.38 ‰	7370.1	19395000	0.07 ‰	1338.3
25-49 years	21896000	0.53 ‰	11626.8	21896000	0.10 ‰	2189.6
50-74 years	16996000	6.84 ‰	116320.6	16996000	2.30 ‰	40688.4
≥ 75 years	4896000	44.60 ‰	218376.3	4896000	17.16 ‰	84025.2
Total	63183000	-	353693.8	63183000	-	128241.5
<b>Standardized rates</b>		<b>5.60 ‰</b>			<b>2.03 ‰</b>	

**Table 3B: Direct cumulative standardization incidence rates of sinus node dysfunction (SND)**

Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Standard UK population Census 2011	Age-specific PPM incidence rates	Expected number of PPM cases in standard UK population	Standard UK population Census 2011	Age-specific PPM incidence rates	Expected number of PPM cases in standard UK population
< 25 years	19395000	0.09 ‰	1799.9	19395000	0.02 ‰	333.6
25-49 years	21896000	0.23 ‰	5110.5	21896000	0.03 ‰	732.8
50-74 years	16996000	2.63 ‰	44634.9	16996000	0.85 ‰	14419.4
≥ 75 years	4896000	14.96 ‰	73235.8	4896000	3.74 ‰	18312.9
Total	63183000	-	124781.1	63183000	-	33797.7
<b>Standardized rates</b>		<b>1.97 ‰</b>			<b>0.53 ‰</b>	

**Table 3C: Direct standardization cumulative incidence rates for atrioventricular block (AVB)**

Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Standard UK population Census 2011	Age-specific PPM incidence rates	Expected number of PPM cases in standard UK population	Standard UK population Census 2011	Age-specific PPM incidence rates	Expected number of PPM cases in standard UK population
< 25 years	19395000	0.26 ‰	5056.3	19395000	0.05 ‰	1000.8
25-49 years	21896000	0.25 ‰	5550.6	21896000	0.05 ‰	1096.9
50-74 years	16996000	3.52 ‰	59820.8	16996000	1.33 ‰	22660.8
≥ 75 years	4896000	26.55 ‰	129974.1	4896000	11.66 ‰	57092.7
Total	63183000	-	200401.8	63183000	-	81851.2
<b>Standardized rates</b>		<b>3.17 ‰</b>			<b>1.30 ‰</b>	

PPM=Permanent Pacemaker; ‰=per thousand

**Table 4: Crude and age-standardized (direct) risk ratios (95% CI) of permanent pacemaker implantation for South Asians compared to Caucasians, May 2006 to March 2014.**

	Crude risk ratios	P value	Age-standardized risk ratios	P value
<b>All age groups</b>				
All indications	0.17 (0.15-0.20)	<0.0001	0.36 (0.36-0.37)	< 0.0001
Sinus node dysfunction	0.14 (0.11-0.19)	< 0.0001	0.27 (0.27-0.28)	< 0.0001
Atrioventricular block	0.19 (0.17-0.23)	< 0.0001	0.41 (0.41-0.42)	< 0.0001
<b>Age ≥ 50 years</b>				
All indications	0.27 (0.23-0.31)	<0.0001	0.38 (0.37-0.38)	< 0.0001
Sinus node dysfunction	0.22 (0.17-0.29)	< 0.0001	0.28 (0.27-0.28)	< 0.0001
Atrioventricular block	0.29 (0.24-0.35)	< 0.0001	0.43 (0.42-0.43)	< 0.0001

Above are risk ratios and 95% confidence intervals

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