RESEARCH ARTICLE

REVISED Changes in prevalence and patterns of consanguinity in Bradford, UK – evidence from two cohort studies

[version 2; peer review: 4 approved, 2 approved with reservations]

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Abstract

Background

Research undertaken using the Born in Bradford cohort study identified consanguinity as a major risk factor for congenital anomalies and also reported longer term adverse health outcomes associated with consanguinity.

Methods

We report the prevalence of consanguinity from two cohort studies in the same geographical area with a nine year gap: Born in Bradford (BiB) and Born in Bradford's Better Start (BiBBS). We examine and compare rates of consanguinity and the characteristics of the consanguineous in each study population to examine if and how these have changed in the years between the recruitment periods of 2007–2010 (BiB) and 2016–2019 (BiBBS).

Results

There had been a substantial decrease in consanguineous unions in women of Pakistani heritage, the proportion of women who were first cousins with the father of their baby fell from 39.3% to 27.0%, and those who were other blood relations fell from 23.1% to 19.3%. Only 37.6% of Pakistani heritage women were unrelated to the father of their baby in BiB, but 53.7% were unrelated in BiBBS. All but one White British respondent was unrelated to their baby's father in both cohorts, and around 90% of the 'Other ethnicities' group (i.e., not White British or Pakistani heritage) were unrelated to the baby's father in both cohorts. The reduction was most marked in women of

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Pakistani heritage who were born in the UK, in those educated to A level or higher and in women under age 25.

Conclusions

An appreciation of changing rates of consanguinity and linked health needs will be valuable to those who commission and provide antenatal, paediatric and genetic services in Bradford and in other areas where consanguinity is likely to be a major risk factor. Falling rates in this city may reflect wider changes in partner choices in similar populations.

Plain language summary

High rates of consanguinity (unions between blood relations, most often cousins) are a major risk factor for a particular category of genetic disorders called recessive disorders. These disorders can have a severe impact on children. There are also other longer term adverse health effects observed in children and adults from these unions. We report results from two ongoing cohort studies from the same city, Born in Bradford (BiB) and Born in Bradford's Better Start (BiBBS). We examine and compare rates of consanguinity and the characteristics of the consanguineous in each study population to examine if and how these have changed in the years between the two cohort recruitment periods of 2007–2010 (BiB) and 2016–2019 (BiBBS).

In both cohorts the majority of women were of Pakistani heritage, 65% and 62% in the BiB and BiBBS respectively. Over a nine year period there had been a reduction in consanguineous unions in the Pakistani heritage cohort members. Only 38% of Pakistani heritage women were unrelated to the father of their baby in the BiB cohort, but 54% were unrelated in the BiBBS cohort. Rates of consanguinity in White British women and women in the "other ethnicities" group were very low in both cohorts. The reduction was most marked in women of Pakistani heritage who were born in the UK, in those educated to A level or higher and in women under age 25.

Comparing cohorts across time is a valuable way to examine social and behavioural change especially where the characteristics of the cohort members are similar. A reduction in consanguinity is likely to reduce the number of recessive genetic disorders and other illnesses linked to consanguinity.

Keywords

cohort studies, consanguinity, congenital anomalies, Pakistani heritage

This article is included in the Born in Bradford gateway.

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Author roles: Small N: Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Kelly B**: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Wright J**: Conceptualization, Funding Acquisition, Methodology, Project Administration, Resources, Writing – Original Draft Preparation, Writing – Review & Editing

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REVISED **Amendments from Version 1**

We have been working on allied and complimentary studies alongside this study. When we posted this article, and when it was sent for review, two key pieces of work were still in development. These are now completed and are available to augment this article. Hence, we have added two additional references to recent work. One refers to health and education outcomes of BiB children analysed according to the consanguinity status of the child's parents (Small *et al.*, 2024a). The second reports a qualitative study examining views about consanguinity and about genetic risk in members of the Pakistani heritage community in Bradford (Small *et al.*, 2024c).

We have rewritten our Plain Language Summary to make it clearer that the considerable majority of children born to consanguineous parents will not have recessive genetic disorders. The new version is more clearly different from the article Abstract and it conforms closely to Wellcome Open guidance re writing such summaries.

We have added an extra paragraph to the introduction to make it clear that the considerable majority of children born to consanguineous parents will not have recessive genetic disorders and to add more detail about other risk factors and other genetic risks. We have made the point that even if the risk is low the consequence can be severe.

We have developed a paragraph in our Discussion in the section "Reasons for a reduction in consanguinity" to include some detail of our qualitative study with members of Bradford's Pakistani heritage community.

We have added an extra paragraph to our Conclusions to develop the key implications of the study, making it more explicit that knowledge of prevalence of consanguinity and trends in how it is changing assist health planners. We have also underlined what a complex social change a shift in marriage choice encompasses.

Any further responses from the reviewers can be found at the end of the article

Introduction: Study background and context

A consanguineous union is one in which the male-female couple are related as second cousins or closer. One billion people, one in eight of the world's population, live in countries where these are common (defined as rates of above 20% – see Bittles, 2012). Frequency of recessive genetic disorders among children born to consanguineous parents is around twice that of children of non-related parents (Sheridan *et al.*, 2013) and there is evidence of increased rates of mortality and morbidity in these children (Bishop *et al.*, 2018; Clark *et al.*, 2019; Lodh *et al.*, 2023; Malawsky *et al.*, 2023; Small *et al.*, 2024a).

Congenital anomalies occur in all communities. Rates are higher in children born to consanguineous parents although even here the considerable majority of children will not have an anomaly. In the BiB study about 3 in every 100 children born to non-consanguineous parents and about 6 in every 100 born to consanguineous partners were born with an anomaly. There are also other significant factors associated with increased presence of congenital anomalies. BiB reported an increase in risk of similar magnitude to consanguinity for non-consanguineous mothers of white British origin older than 34 years. Further, anomalies of different sorts and with risk factors other than consanguinity occur in all babies (Sheridan *et al.*, 2013). But even though congenital anomalies occur in only a small proportion of children, the consequences of being born with one can be severe (Small *et al.*, 2024a). These consequences include the death of the child or long-term morbidity. Given that there are high numbers of consanguineous parents in Bradford, and despite most of their children not having a congenital anomaly, the numbers dying or living with the consequences of a congenital anomaly in Bradford are significant to the city and to its health services.

We report the prevalence of consanguinity and the characteristics of the consanguineous from two ongoing UK birth cohort studies in Bradford, a city in the north of England, with a nine year gap: Born in Bradford (BiB), recruited between 2007 and 2010 (Wright *et al.*, 2013), and Born in Bradford's Better Start (BiBBS), recruited between 2016 and 2019 (Dickerson *et al.*, 2022).

Methods

Data

Between 12th March 2007 and 24th December 2010 BiB collected detailed information from 12453 women with 13776 pregnancies and from 3448 of their partners (Raynor & The Born in Bradford Collaborative Group, 2008; Wright *et al.*, 2013). A second cohort, BiBBS, was recruited between 4th January 2016 and 30th November 2019. It was made up of pregnant women living in three inner city wards, Bowling and Barkerend, Bradford Moor and Little Horton, all of which are within the wider BiB recruitment area (Dickerson *et al.*, 2016; Dickerson *et al.*, 2022). There were 2392 women recruited with 2626 pregnancies in the BiBBS cohort; 2494 women in BiB were in the Better Start area. (See Small *et al.*, 2024b for a comparison of the characteristics of the total BiB cohort compared with the BiB women in the Better Start Area.) Data is at the pregnancy level, and some women had more than one pregnancy during each recruitment period. The relationship with the father of the baby could change between pregnancies for woman with more than one pregnancy. Also, a small number of women are in both cohorts including 237 women of Pakistani heritage.

In both cohorts the consanguinity status of women was captured in a self-administered questionnaire (see Small *et al.*, 2024b for relevant sections of each questionnaire). Women were classified as not related, first cousin, or other blood relation with the father of their child. Not all gave full answers to these questions and we exclude these from the subsequent analysis. The resulting figure in each cohort sees 2494 women in the BiB cohort in the Better Start area and 2564 in BiBBS. These constitute the sample used in this paper.

Other measures captured in both cohorts' recruitment questionnaires and used in this analysis were ethnicity, age of woman at pregnancy, country of birth and age that women born outside the UK moved to the UK, self-reported financial status,

and education. Ethnicity was grouped into three categories: White British, Pakistani heritage, and other ethnicity. Self-reported financial status was captured using a five-point Likert scale. Due to small numbers, we grouped the self-reported financial status categories of 'finding it quite difficult' and 'finding it very difficult' into a single category in this analysis. The education status of women educated outside the UK was equivalised to UK education levels, and as questions on women's education status were slightly different in each cohort they were grouped to a comparable dichotomous measure of A-level or above and below A-level. Achieving A-level or above requires continuing in education post age 16 years, and this has been identified as a key measure of educational inequalities (Tackey *et al.*, 2011).

Analysis plan

We present a description of the characteristics of each cohort. We then look at consanguinity status by ethnicity for each cohort, illustrating any changes that occurred between the cohorts. Next we explore changes in consanguinity status for Pakistani heritage women. We estimate their rates of consanguinity by cohort characteristics with 95% confidence intervals: looking at age at pregnancy, self-reported financial status, and women's education. We also look at rates by a combined measure of country of birth and age moved to the UK if women were born outside the UK. Results are presented in tables for each cohort and illustrated in figures comparing rates. This analysis enables us to determine how consanguinity status varies by these characteristics within each cohort, and also crucially what differences exist between the two cohorts; thereby allowing us to examine change in consanguinity status for Pakistani heritage women over time in a fixed geographical area.

After presenting these rates we then model consanguinity status. We employ multinomial regression models which look at consanguinity status for Pakistani heritage women, all data from both cohorts being combined in a single dataset for the analysis. First these models considered cohort, country of birth, women's age at pregnancy, self-reported financial status, and women's education individually in five separate univariable regression models. Then all five measures are included in a single multivariable regression model. In this section of the analysis, we used country of birth rather than the combined country of birth and age moved to UK measures, as age at pregnancy and age moved to UK from Pakistani are related (many women aged under 25 years at pregnancy could not have moved to the UK aged 25 and over). The univariable models are analogous with the descriptive analysis presented in Table 1. These univariable models are presented in order to compare them with the results of the multivariable model. Essentially the size of the effect for cohort in the univariable model estimates the observed differences between cohorts, and the size of the effect for cohort in the multivariable model estimates what the cohort effect would be if all other characteristics were held constant, i.e., controlling for the changes in these characteristics that occurred between the two cohorts. We also consider area level change that may have occurred between the time points of both cohorts. All statistical analysis was carried out using Stata 17 (StataCorp, 2023).

Table 1. Cohort characteristics and consanguinity status for Pakistani heritage women. BiB, Born in Bradford; BiBBS, Born in Bradford's Better Start.

	BiB in Better Start area					BiBBS				
Cohort characteristic	**Total n**	**First cousins Percent (95% CI)**	**Other blood relation Percent (95% CI)**	**Not related Percent (95% CI)**	**Total percent**	**Total n**	**First cousins Percent (95% CI)**	**Other blood relation Percent (95% CI)**	**Not related Percent (95% CI)**	**Total percent**
Age of woman at pregnancy (grouped)										
Under 25	508	42% (38%-46%)	23% (20%-27%)	35% (31%-39%)	100%	252	28% (23%-34%)	19% (15%-25%)	53% (47%-59%)	100%
25 to 29	546	41% (37%-45%)	22% (19%-25%)	37% (33%-41%)	100%	486	25% (21%-29%)	19% (15%-22%)	56% (52%-61%)	100%
30 to 34	363	37% (32%-42%)	22% (18%-27%)	41% (36%-46%)	100%	500	26% (23%-30%)	22% (19%-26%)	52% (47%-56%)	100%
35 and over	180	31% (24%-38%)	29% (23%-36%)	41% (34%-48%)	100%	313	30% (26%-36%)	16% (13%-21%)	53% (48%-59%)	100%

Cohort characteristic	BiB in Better Start area					BiBBS				
	Total n	First cousins Percent (95% CI)	Other blood relation Percent (95% CI)	Not related Percent (95% CI)	Total percent	Total n	First cousins Percent (95% CI)	Other blood relation Percent (95% CI)	Not related Percent (95% CI)	Total percent
Combined country of birth and aged moved to UK										
Born UK	610	36% (32%-40%)	23% (20%-27%)	41% (38%-44%)	100%	707	20% (17%-23%)	16% (13%-19%)	64% (61%-68%)	100%
Born Pakistan: moved to UK under 16 yrs.	188	40% (33%-47%)	26% (20%-32%)	34% (27%-41%)	100%	131	33% (25%-41%)	17% (10%-23%)	50% (42%-59%)	100%
Born Pakistan: moved to UK 16 to 19 yrs.	226	51% (45%-58%)	21% (16%-27%)	27% (22%-33%)	100%	157	41% (34%-49%)	20% (14%-26%)	39% (31%-47%)	100%
Born Pakistan: moved to UK 20 to 24 yrs.	350	40% (35%-45%)	24% (19%-28%)	36% (31%-41%)	100%	300	36% (30%-41%)	25% (20%-30%)	39% (34%-44%)	100%
Born Pakistan: moved to UK 25 yrs. plus	171	30% (23%-37%)	22% (16%-28%)	49% (41%-56%)	100%	220	26% (20%-31%)	24% (18%-30%)	51% (44%-58%)	100%
Self-reported financial status										
Living comfortably	384	40% (35%-45%)	23% (19%-28%)	37% (32%-42%)	100%	608	27% (24%-31%)	22% (19%-26%)	51% (47%-55%)	100%
Doing alright	673	39% (35%-43%)	24% (21%-27%)	37% (34%-41%)	100%	593	27% (24%-31%)	19% (16%-22%)	54% (50%-58%)	100%
Just about getting by	398	39% (35%-44%)	25% (21%-30%)	36% (31%-41%)	100%	194	31% (25%-38%)	16% (11%-22%)	53% (46%-60%)	100%
Quite/ very difficult	127	38% (30%-47%)	14% (9%-21%)	48% (39%-57%)	100%	83	22% (14%-32%)	13% (7%-22%)	65% (54%-75%)	100%
Women's education status										
A-level or higher	562	32% (28%-36%)	19% (15%-22%)	50% (46%-54%)	100%	714	23% (20%-26%)	17% (14%-20%)	60% (56%-64%)	100%
Lower than A-level	967	43% (40%-46%)	26% (23%-28%)	31% (28%-34%)	100%	769	30% (27%-33%)	21% (18%-24%)	49% (46%-52%)	100%

Results

Sample characteristics

Table 2 presents characteristics of the BiB cohort in the Better Start area and the BiBBS cohort. (For the sake of brevity, in the remainder of the text the 'BiB cohort in the Better Start area' will simply be referred to as the 'BiB cohort'.) In both cohorts the majority of women were of Pakistani heritage, 64.8% and 61.6% in the BiB and BiBBS respectively. BiBBS women were older at the birth of their child, better educated and more financially secure.

Table 2. Characteristics of BiB cohort in the Better Start area, and BiBBS cohort. BiB, Born in Bradford; BiBBS, Born in Bradford's Better Start.

Cohort characteristics	BiB in the Better Start area (n = 2,494)		BiBBS (n = 2,564)	
	n	Percentage (95% CI)	n	Percentage (95% CI)
Ethnicity				
White British	441	17.7% (16.3%-19.3%)	296	11.6% (10.4%-12.9%)
Pakistani heritage	1,615	64.8% (62.9%-66.7%)	1,571	61.6% (59.7%-63.5%)
Other ethnicity	435	17.5% (16.0%-19.0%)	683	26.8% (25.1%-28.5%)
Missing	3		14	
Age of woman at pregnancy				
Under 20	181	7.3% (6.3%-8.3%)	67	2.6% (2.1%-3.3%)
20 to 24	725	29.1% (27.3%-30.9%)	476	18.6% (17.1%-20.1%)
25 to 29	827	33.2% (31.3%-35.0%)	800	31.2% (29.4%-31.4%)
30 to 34	506	20.3% (18.8%-21.9%)	759	29.6% (27.9%-31.4%)
35 and over	255	10.2% (9.1%-11.5%)	462	18.0% (16.6%-19.5%)
Mean (SD)		26.9 (5.4)		29.3 (5.5)
Whether born in UK				
No	1,288	51.7% (49.7%-53.6%)	1,382	54.1% (52.2%-56%)
Yes	1,205	48.3% (46.4%-50.3%)	1,173	45.9% (44%-47.8%)
Missing	1		9	
Self-reported financial status				
Living comfortably	579	23.5% (21.9%-25.2%)	877	35.9% (34.0%-37.9%)
Doing alright	1,013	41.1% (39.2%-43.1%)	995	40.8% (38.8%-42.7%)
Just about getting by	643	26.1% (24.4%-27.9%)	398	16.3% (14.9%-17.8%)
Quite difficult	174	7.1% (6.1%-8.1%)	127	5.2% (4.4%-6.2%)
Very difficult	56	2.3% (1.8%-2.9%)	44	1.8% (1.3%-2.4%)
Missing	29		123	
Women's education status				
A-level or higher	850	36.5% (34.5%-38.4%)	1,061	44.8% (42.8%-46.8%)
Lower than A-level	1,481	63.5% (61.6%-65.5%)	1,307	55.2% (53.2%-57.2%)
Missing	163		196	

Has there been a change in the number of consanguineous relationships recorded in the two cohorts?

Table 3 gives details of the rates of consanguinity for both cohorts by ethnicity. Rates in White British women were almost zero; and in "other ethnicity" women (not White British or Pakistani) they were similar in the two cohorts, 11.0% in BiB and 11.7% in BiBBS. Overall, there has been a substantial decrease in consanguineous relationships between the two survey periods consequent on reductions in the Pakistani heritage group. In the BiB cohort 37.6% of Pakistani heritage women were unrelated to the father of their child, and 53.7% were unrelated in the BiBBS cohort (see Figure 1)

Table 3. Consanguinity status for pregnancies by ethnicity in the BiB and BiBBS cohorts. BiB, Born in Bradford; BiBBS, Born in Bradford's Better Start.

Ethnicity and consanguinity status	BiB		BiBBS	
	n	Percentage (95% CI)	n	Percentage (95% CI)
All				
Not related	1,429	57.8% (55.8%-59.7%)	1,724	68.4% (66.5%-70.1%)
First cousins	659	26.6% (24.9%-28.4%)	462	18.3% (16.9%-19.9%)
Other blood relation	386	15.6% (14.2%-17.1%)	336	13.3% (12.1%-14.7%)
Missing	20		42	
Total	2,494	100%	2,564	100%
White British				
Not related	439	99.8% (98.4%-100.0%)	294	99.7% (97.6%-100.0%)
First cousins	1	0.2% (0.0%-1.6%)	1	0.3% (0.0%-2.4%)
Other blood relation	0		0	
Missing	1		1	
Total	441	100%	296	100%
Pakistani heritage				
Not related	601	37.6% (35.5%-40.0%)	833	53.7% (51.2%-56.2%)
First cousins	627	39.3% (36.9%-41.7%)	418	27.0% (24.8%-29.2%)
Other blood relation	369	23.1% (21.1%-25.2%)	300	19.3% (17.4%-21.4%)
Missing	18		20	
Total	1,615	100%	1,571	100%
Other ethnicity				
Not related	387	89.0% (85.6%-91.6%)	593	88.4% (85.7%-90.6%)
First cousins	31	7.1% (5.1%-10.0%)	42	6.3% (4.7%-8.4%)
Other blood relation	17	3.9% (2.4%-6.2%)	36	5.4% (3.9%-7.4%)
Missing	0		12	
Total	435	100%	683	100%

Consanguinity status of Pakistani heritage women by characteristics in both cohorts

We combined country of birth and the age that women who were born in Pakistan moved to the UK into a single measure, Table 4 indicates the numbers in these categories in each cohort. In the BiBBS cohort a higher proportion of Pakistani heritage women were born in the UK, and the women who were born in Pakistan were more likely to have moved to the UK at an older age.

Differences in consanguinity status for Pakistani heritage women by characteristics are reported in Table 3 for both cohorts. The largest differences between the two cohorts are for first cousins and those not related by blood. For ease of comparison, proportions of Pakistani heritage women who were first cousins with the father of their child, and the proportion were not blood related are illustrated in Figure 2 and Figure 3 respectively.

Figure 2 illustrates differences in the proportion of first cousin relationships between the BiB and BiBBS cohort by characteristics, as well as illustrating the differences within each cohort. There was a lower proportion of first cousins in the BiBBS cohort for all age groups apart from women aged 35 years and over. The biggest difference was for the younger women. There is a substantial fall between the BiB and BiBBS cohort in the

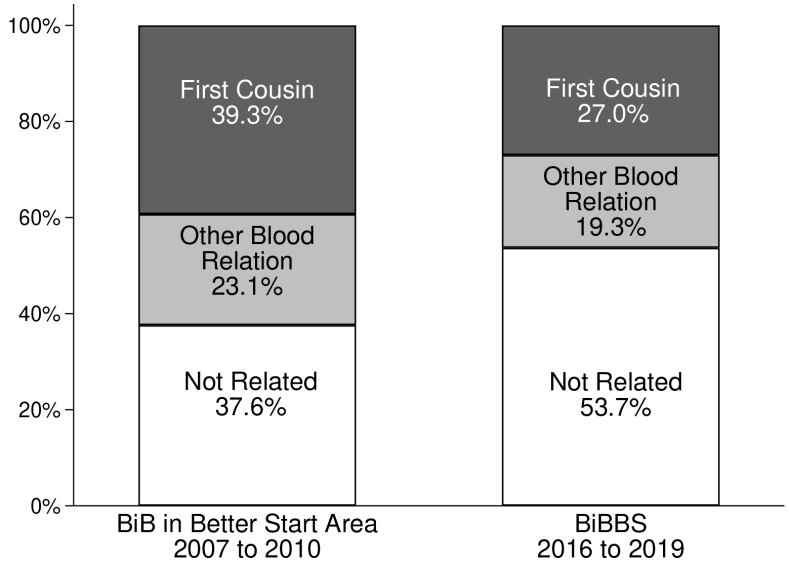

Figure 1. Consanguinity status for Pakistani heritage women in the BiB cohort in Better Start area and the BiBBS cohort. BiB, Born in Bradford; BiBBS, Born in Bradford's Better Start.

Table 4. Combined country of birth and age moved to UK for Pakistani heritage women.

Combined country of birth and age moved to the UK for Pakistani heritage women	BiB		BiBBS	
	n	Percentage	n	Percentage
Born UK	610	39.5%	707	46.7%
Born in Pakistan: moved to UK aged under 16 yrs.	188	12.2%	131	8.6%
Born in Pakistan: moved to UK aged 16 to 19 yrs.	226	14.6%	157	10.4%
Born in Pakistan: moved to UK aged 20 to 24 yrs.	350	22.7%	300	19.8%
Born in Pakistan: moved to UK aged 25 yrs.	171	11.1%	220	14.5%
Born other country/ missing	52		36	
Total	1597	100.0%	1551	100.0%

proportion of first cousin relationships in Pakistani heritage women who were born in the UK. There were also lower rates of first cousins for all women born in Pakistan regardless of the age they came to the UK, but these were small differences with overlapping 95% confidence intervals. The highest proportion of women who were in first cousin relationships was observed in women born in Pakistan who moved to the UK aged 16 to 19 years. There are differences between the cohorts for women who reported they were financially "living comfortably" and for those who reported they were 'doing alright' with the percentage in a first cousin union lower in BiBBS in both categories. Finally, Figure 2 illustrates that the proportion of Pakistani heritage women in first cousin relationships was lower for women with higher educational status within both cohorts. In terms of differences between cohorts, the BiBBS cohort had a lower proportion of women who were first cousins with the father of their child in both educational status groups.

Table 2 had indicated that overall, the proportion of Pakistani heritage women who were other blood relation with the father of their child was slightly lower in the BiBBS cohort, compared to the BiB cohort. Table 4 shows that there were no differences within the BiB cohort, apart from by women's education, where fewer women with A-level or higher were other blood relations, compared to women who had lower than A-level education. There were no differences within the BiBBS cohort. There were only two differences between the BiB and

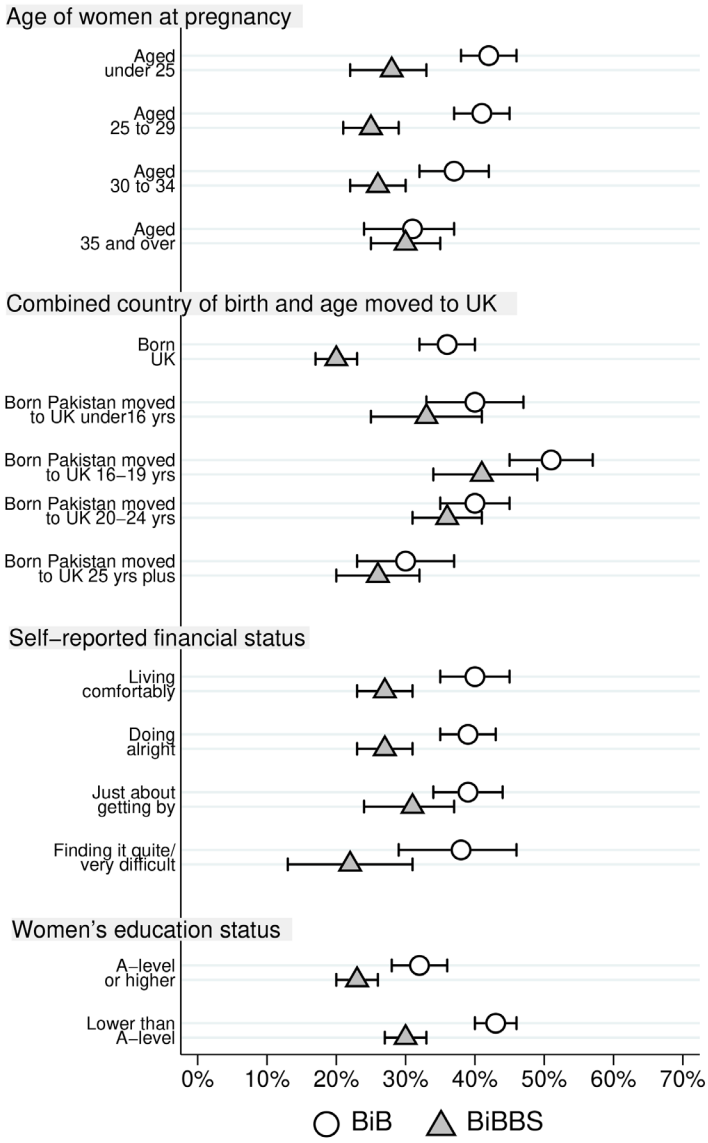

Figure 2. Percentage of Pakistani heritage women who are first cousins with the father of their child by cohort characteristics (with 95% confidence intervals).

BiBBS cohorts in the proportion of Pakistani heritage women who are other blood relation with the father of their child; fewer women aged 35 and over and fewer women born in the UK were other blood relations in BiBBS compared to BiB.

Figure 3 illustrates differences in the proportion of women not related by blood between the BiB and BiBBS cohort, and the differences within each cohort. There are relatively little differences by age group within each cohort, but large differences between the two cohorts. Figure 3 also illustrates that the largest difference between the two cohorts in the proportion not related by blood was for Pakistani heritage women born in the UK, and for women born in Pakistan who moved to the UK under the age of 16 years. There was no difference for women who were born in Pakistan who moved to the UK at an older age. The proportion of Pakistani heritage women not related by blood to the father of their child was higher in BiBBS than BiB for all self-reported financial status groups; these differences were substantive, apart from those finding it 'quite/ very difficult', where there were large overlapping confidence intervals for this group.

Consanguinity status of Pakistani heritage women in the context of differences between cohorts

We saw in Table 2 that there were differences in the characteristics of women in the BiB and BiBBS cohort. (See Small *et al.*, 2024b for more detail, specifically the changes

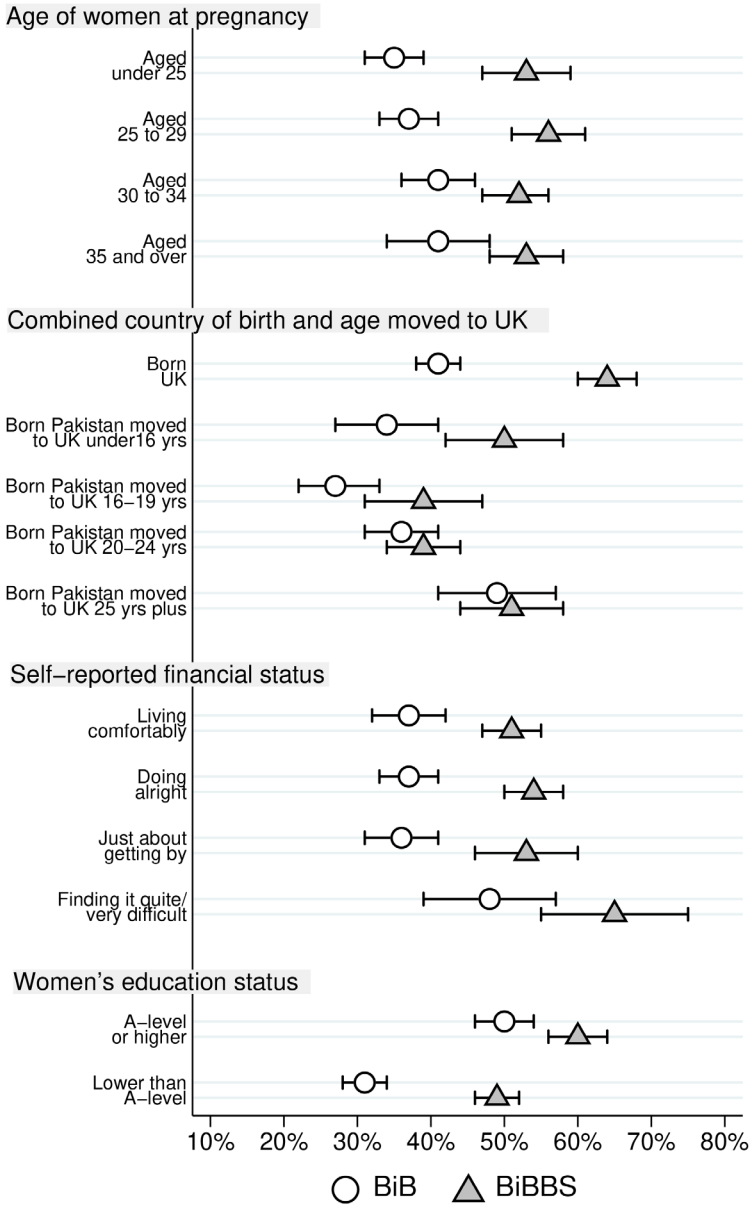

Figure 3. Percentage of Pakistani heritage women who are not related by blood to the father of their child by cohort characteristics (with 95% confidence intervals).

in age at pregnancy, country of birth, self-reported financial status, and education status broken down by ethnicity.) Compared to the BiB cohort Pakistani heritage women in the BiBBS cohort were more likely to be all of following; older at pregnancy, born in the UK, to self-report better financial status, and to have higher education status.

To what extent do these changes contribute to the observed differences in consanguinity status for Pakistani heritage women between the two cohorts? The results from multinomial regression models are presented in Table 5 as relative risk ratios (RRR) with 95 percent confidence intervals (95% CI). The relative risk ratios are presented in relation to the reference category for each variable; results for first cousin relationships and other blood relations are shown (the base reference outcome being women not related by blood to the father of their child).

In the separate univariable model Pakistani heritage women in the BiB cohort had twice the probability of being first cousins with the father of their child compared to the BiBBS cohort. This ratio reduced very slightly in the multivariable models, after controlling for other characteristics. Also, Pakistani heritage women in the BiB cohort had a higher

Table 5. Results for separate univariable and combined multivariable multinomial regression models presented as relative risk ratios (base outcome = not related). BiB, Born in Bradford; BiBBS, Born in Bradford's Better Start.

		Relative Risk Ratio (RRR)			
		Univariable		Multivariable	
		RRR	(95% CI)	RRR	(95% CI)
		First cousin			
Cohort					
	BiBBS (reference)	1.00		1.00	
	BiB in Better Start area	2.08	(1.77-2.45)	1.82	(1.51-2.18)
Combined country of birth and age moved UK					
	Born in UK (reference)	1.00		1.00	
	Not born in UK	1.84	(1.55-2.17)	1.68	(1.40-2.01)
Age of woman at pregnancy					
	Under 25 (reference)	1.00		1.00	
	25 to 29	0.80	(0.65-0.99)	0.88	(0.70-1.11)
	30 to 34	0.72	(0.57-0.89)	0.76	(0.59-0.98)
	35 and over	0.69	(0.53-0.89)	0.73	(0.54-0.98)
Self-reported financial status					
	Living comfortably (reference)	1.00		1.00	
	Doing alright	1.05	(0.86-1.27)	0.92	(0.75-1.13)
	Just about getting by	1.25	(0.99-1.58)	0.99	(0.77-1.28)
	Quite/ very difficult	0.82	(0.58-1.14)	0.61	(0.42-0.88)
Women's education status					
	A-level or above (reference)	1.00		1.00	
	Lower than A-level	1.98	(1.68-2.35)	1.77	(1.48-2.12)
		Other blood relation			
Cohort					
	BiBBS (reference)	1.00		1.00	
	BiB in Better Start area	1.70	(1.42-2.05)	1.64	(1.33-2.02)
Whether born in UK					
	Born in UK (reference)	1.00		1.00	
	Not born in UK	1.58	(1.31-1.91)	1.49	(1.22-1.83)
Age of woman at pregnancy					
	Under 25 (reference)	1.00		1.00	
	25 to 29	0.82	(0.64-1.06)	0.93	(0.71-1.22)
	30 to 34	0.88	(0.68-1.13)	0.97	(0.74-1.29)
	35 and over	0.80	(0.60-1.08)	0.92	(0.66-1.28)
Self-reported financial status					
	Living comfortably (reference)	1.00		1.00	

		Relative Risk Ratio (RRR)			
		Univariable		Multivariable	
		RRR	(95% CI)	RRR	(95% CI)
	Doing alright	0.95	(0.76-1.18)	0.86	(0.69-1.08)
	Just about getting by	1.08	(0.83-1.40)	0.85	(0.63-1.13)
	Quite/ very difficult	0.51	(0.33-0.79)	0.40	(0.25-0.63)
Women's education status					
	A-level or above (reference)	1.00		1.00	
	Lower than A-level	1.88	(1.55-2.28)	1.76	(1.44-2.16)

probability of being other blood relations in the univariable models compared to the BiBBS cohort; this also remained similar in the multivariable models after controlling for other measures.

For the other measures the model results are similar to the results observed in the analysis previously presented, except for a finding related to self-reported financial status. In the multivariable models those who reported that their financial status was quite or very difficult had a lower probability of being first cousin and other blood relation compared to those who reported 'living comfortably'. Previous descriptive analysis had suggested women who reported finding their financial situation 'quite/ very difficult' were less likely to be related by blood to the father of their child (see Figure 3), but these differences were not conclusive due to large confidence intervals. The analysis utilising regression models combine both cohorts into a single dataset, and so have more power to detect these differences.

To summarise, when we looked at multinominal regression models examining the probability of Pakistani heritage respondents being in consanguineous relationships, considering differences by cohort and by what age respondents came to the UK, we found that consanguineous relationships were highest amongst those born outside the UK who moved to the UK when aged between 16 and 19 years of age: the lowest rates were for those born in the UK.

We found that between the BiB and BiBBS cohorts, there was a large increase in the percentage of Pakistani heritage respondents born in the UK who were not related (from 40.5% to 64.2%), and a smaller increase for Pakistani heritage respondents born outside the UK but who came to the UK before the age of 16 (from 33.5% to 50.4%). There were also increases for Pakistani heritage respondents who were born outside the UK and came to the UK after the age of 16 years, but these were small, with overlapping confidence intervals. For first cousin relationships there was an overall reduction between the two cohorts, driven by a large reduction amongst Pakistani heritage respondents born in the UK (from 36.2% to 19.8%).

Area level change

Around 50% of the White British children born in the Better Start area had moved out by the age of 5, compared to 15% of Pakistani heritage children. These high levels of outward migration should be seen in the context of the Better Start area being relatively small geographically, with a population of about 60,000 people (see Small *et al.*, 2024b). White British families are poorer and are more transient than the Pakistani heritage families. This relative stability suggests that the Pakistani heritage community in the Better Start area may be more comparable over time than the White British group, and certainly more comparable than the diverse "other ethnicity" group.

Discussion

Efforts to raise awareness of genetic risk

Throughout the period covered by BiB and BIBBs health commissioners and providers in Bradford have been well aware of the high rates of recessive disorders and their attendant impacts on mortality and morbidity and they had been concerned to develop health promotion, heath education and care initiatives in response (see reports from The City of Bradford Joint Strategic Needs Assessments – www.jsna.bradford.gov.uk and from the City of Bradford Child Death Overview Panel – www.bradford.moderngov.co.uk). However, the Department of Health (2010 and 2012) and Khan *et al.* (2010) report that knowledge of genetic risk and service uptake among communities at higher risk of recessive conditions due to consanguinity was poor. By 2016 there was more attention being paid to local initiatives where responses to consanguinity and genetic risk had been developed (Salway *et al.*, 2016) and moves to build a consensus about what health policy and practice was required were underway at a national level (Salway *et al.*, 2019).

In Bradford there was considerable publicity across a range of media, including local media, attendant on the

publication of Born in Bradford's paper about rates of recessive disorder and links to consanguinity in the BiB cohort (Sheridan *et al.*, 2013: https://www.bbc.co.uk/news/uk-england-leeds-23183102.) The size and longevity of BiB means it is well-known in the city - in the years BiB recruited to the study over half the age cohort of children in the city were participants, as were their mothers and some of their fathers. As well as contact to collect data there were regular updates on research findings sent to participant families and many meetings and events where the messages from BiB were shared with the wider metropolitan population. A research study with reach such as this will impact on levels of knowledge about risks to health and may change choices people make about health related behaviours (see Quick *et al.*, 2017). As well as a possible direct effect, BiB also encourages and supports local health services to address issues it has highlighted and provides robust local data to underpin their work. Voluntary sector and faith based organisations also become better informed about the issues. BiB may then be both a direct link to change and a catalyst for change in other organisations policies and priorities and this, in turn, contributes to extending informed choice in the community, enhancing healthy choices and supporting evidence based health provision.

Our data is drawn from a specific area of one city in the north of England, and that city has been the site of this enhanced engagement with understandings of genetic risk. In consequence the choices made by its Pakistani heritage community may be specific to residents of this city and not generalisable to other communities of Pakistani heritage in the UK and elsewhere.

Some potential weaknesses in our data can be noted

Consanguinity is self-reported. There was a high level of completion of questions about consanguinity, indicating that respondents knew their status and were willing to share it. Interviewers were trained and experienced and, in BiB, some family trees were also collected from study recruits and, when analysed, these showed a close link with questionnaire data (Sheridan *et al.*, 2013). It is unlikely that any over or under reporting of consanguinity status would vary between the two time periods our cohorts draw on. Biraderi was not asked in the BiBBS survey so is not considered in the models considering differences between the cohorts (see Bittles & Small, 2016: and Small *et al.* (2017) on the importance of biraderi as an example of endogamy). Age at marriage, year of marriage or age/year when they entered a relationship with their partner was not asked in BiB or BiBBS. We also do not know year of betrothal – i.e., the year when decisions were made to marry a cousin or to marry a non-related person. We have information about previous parity, but not about the date of birth of the respondents first child (if they have children prior to the pregnancy that was included in each study).

Two cohort analysis

An innovative aspect of our approach is the use of two cohorts recruited from the same geographical area but separated by time. For this approach to be of maximum value we must identify that the areas and the characteristics of the population of interest stayed similar and there was continuity in the broad details of the wider social, political and economic context. Small *et al.*, 2024b provides some Census data from 2011 and 2022 in order to situate our findings within this wider context. We would argue that our approach expands the methodological possibilities for longitudinal research. Wadsworth and Bynner (2011) discuss how cohort studies in different time periods can give an indication about patterns of social change. Design of longitudinal studies which compare variables of interest across separate cohorts is greatly aided by using standardised data collection approaches, as in the cohorts we draw on. Comparing cohorts also extends the uses of valuable data willingly given by cohort members.

Reasons for reductions in consanguinity

Our data suggests some key areas to be explored but, in itself, does not explain why there has been a reduction. We have carried out qualitative research to explore reasons why members of the Pakistani heritage community in the city think rates of consanguinity might have changed over time. This qualitative research considers involvement in education, changes in migration patterns and differences in partner choices depending on age of women alongside other factors that were raised by our participants. We also looked at more distal factors including changes in economic wellbeing and shifts in the law and regulations shaping migration to the UK (Small *et al*., 2024c).

Data collection for the BiBBS cohort finished in November 2019. The distribution of changes in rates of consanguinity by age of women, with larger reduction in the rates of consanguineous relationships for women giving birth at a younger age and relatively stable rates in women giving birth at an older age, may indicate that the falls we report are part of a social change in Bradford's Pakistani heritage population and a concomitant downward trajectory in consanguinity. If this is the case by the date of publication we might expect lower rates than we report from births up to 2019.

Conclusions

In a relatively short time period, there has been a drop in the proportion of Bradford women of Pakistani heritage in consanguineous relationships. We have found this out by looking at two groups from the same small geographical area, each recruited into ongoing cohort studies. The area they are recruited from has changed in some of its characteristics – but the change for women of Pakistani heritage has been of a degree that allows us to be confident we are comparing like-with-like groups.

A majority of Pakistani heritage women in BiB were in consanguineous relationships (62.4%). In BiBBS Pakistani heritage women in consanguineous relationships were in a minority (46.3%). This is a substantial drop in a long-established practice in just nine years. Drops in consanguinity are

linked with changes in the rates of consanguinity in women born in the UK or who came to the UK as children. A change in numbers educated to A level and beyond is important. Drops are large in Pakistani heritage women under 25 years at the birth of their child where the fall in first cousin unions is from 41.9% to 27.8%. Consanguinity rates in the over 35's were about the same in both cohorts.

Knowledge of consanguinity prevalence and trends, and the detailed characteristics of who is in consanguineous unions, helps identify at-risk populations, and this can be used to enhance risk awareness and to help target genetic counselling.

The identification of the reductions in consanguinity we report, in particular the considerable reductions in younger people, underscore a complex interplay of cultural, social, and demographic factors. It may be that we are seeing generational changes, and newly evolving societal norms. But these changes need to be monitored to see if they are indications of a lasting change and they need to be considered in other settings where consanguinity is common to see how widespread these reductions in consanguinity are.

A drop in the prevalence of consanguinity is likely to lead to a reduction in recessive genetic disorders and in the high rates of morbidity and mortality evident in children of consanguineous parents in Bradford. If the drop we have identified is replicated in other areas with Pakistani heritage communities our findings will be significance for families from these communities and also for health planning and care provision.

Ethics and consent

Ethical approval has been obtained from the Bradford Research Ethics Committee (Ref 07/H1302/112) for BiB (approval letter dates 1/4/2008). and by Bradford Leeds NHS Research Ethics Committee (15/YH/0455) for BiBBS (approval letter dated 2/11/2015). Research governance approval has been provided from Bradford Teaching Hospitals NHS Foundation Trust. All participants in both cohorts were given Participant Information Sheets approved by the respective ethics committees before recruitment and all participants signed Consent Forms that included consent for data storage, data usage and data sharing.

Data availability

Underlying data

Researchers are encouraged to make use of the BiB and BiBBS data, which are available through a system of managed open access. Before you contact us, please make sure you have read our Guidance for Collaborators. Our BiB Executive reviews proposals on a monthly basis and we will endeavour to respond to your request as soon as possible. You can find out about the different datasets in our Data Dictionary. If you are unsure if we have the data that you need, please contact a member of the BiB team (borninbradford@bthft.nhs.uk).

Once you have formulated your request please complete the 'Expression of Interest' form available here and send to borninbradford@bthft.nhs.uk. If your request is approved we will ask you to sign a Data Sharing Contract and a Data Sharing Agreement, and if your request involves biological samples we will ask you to complete a material transfer agreement.

Extended data

Harvard Dataverse: Changes in prevalence and patterns of consanguinity in Bradford, UK – evidence from two cohort studies: Extended material. https://doi.org/10.7910/DVN/F57B2I (Small *et al.*, 2024b).

Extended data contains additional analysis, providing contextual data of the study population, including 2011 and 2021 UK Census data comparing the populations in the study area to the wider Bradford area and England as a whole.

We ensured our reporting met the STROBE guidelines for observational studies. Specifically, we have used the cross sectional STROBE guidelines, rather than the cohort guidelines, as our paper essentially uses a comparison between two cross sectional datasets (von Elm *et al.*, 2007).

Author contribution

All authors contributed to the study design and methodology. BK did formal analysis. NS wrote the first draft of the manuscript. All authors reviewed, revised and approved the manuscript.

Acknowledgments

Born in Bradford and Born in Bradford's Better Start are only possible because of the enthusiasm and commitment of the children and parents in BiB. We are grateful to all the participants, health professionals and researchers who have made Born in Bradford happen.

We gratefully acknowledge the contribution of TPP and the TPP ResearchOne team in completing study participant matching to GP primary care records and in providing ongoing informatics support.

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Open Peer Review

Current Peer Review Status: ✔ ✔ ? ? ✔ ✔

Version 2

Reviewer Report 27 January 2025

https://doi.org/10.21956/wellcomeopenres.25901.r115504

✔ **Babak Khoshnood**
INSERM Centre de Recherche Épidémiologie et Statistique, Paris, France

Thank you for the opportunity to read and review this interesting manuscript. The article has already gone through a couple of reviews and I find the current version an accurate and well-written report of an interesting and useful study. I only have a few remarks, which I hope the authors find helpful in possibly revising the article.

There is mention that the overall risk of congenital anomalies (CA) was twice as high for newborns of mothers in consanguineous couples than those who were not (6 vs. 3 %). This requires some clarification and explanation as follows:

Are these total or live birth prevalence figures? If they are total prevalence figures the finding is at least somewhat surprising. As the authors point out, the risk of (autosomal) recessive genetic disorders is higher (twice as high) in cases of consanguinity. However, to my knowledge, this is not true of other anomalies including those without clearly known genetic inheritance patterns. Hence, one would not expect a two-fold increase in the OVERALL risk of CA associated with consanguinity.

If these figures refer instead to live birth prevalence, one possible / partial explanation for the two-fold difference may be that in addition to consanguinity resulting in a two-fold higher prevalence of recessive genetic disorders, due to associations perhaps with socioeconomic factors including maternal education, the probability of prenatal diagnosis and Terminations of Pregnancy for Fetal Anomalies (TOPFA) may be different in relation to consanguinity. Therefore, the two-fold higher OVERALL risk of CA may be due to higher TOPFA for cases not associated with consanguinity.

A perhaps useful "back of the envelope" calculation of expected changes in attributable fractions in the risk of CA related to consanguinity as a result of the decrease in consanguineous unions may make a useful addition to the paper but I defer to authors as to whether this is really necessary.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology of congenital anomalies, in particular Down syndrome, neural tube and congenital heart defects

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 02 January 2025

https://doi.org/10.21956/wellcomeopenres.25901.r115509

Grace (Qun) Miao
Better Outcomes Registry & Network (BORN) Ontario, Children's Hospital of Eastern Ontario, Ottawa, Canada

It is a interesting topic. The study was well designed and well written. The authors have made revisions to the manuscript. The quality has been improved significantly. I don't have any comments. It is ready for indexing. The table and graphs presented clearly. The conclusions drawn adequately supported by the results.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: maternal and child health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 02 January 2025

https://doi.org/10.21956/wellcomeopenres.25901.r115510

?

Julian Little
Epidemiology & Community Medicine, University of Ottawa, Ottawa, Canada

This manuscript reports on the prevalence of consanguinity in two sets of participants from the Bradford area, one recruited in 2007-2010, the other in 2016-9. A decline in prevalence was reported. The earlier data set was larger because it covered a larger geographical area. The analysis in the present manuscript was restricted to cover the same geographical sub area in which the second set of participants were recruited. Reference is given to another paper in which the subset and total population in the first period are compared - it would have been helpful to present summary of the results of the comparison.

The manuscript seems timely as consanguinity has been discussed in the UK Parliament recently (articles by Matthew Syed, The Times, 15 December 2024 and 9 April 2024) and there have been moves to pass legislation in some Scandinavian countries (https://www.dailymail.co.uk/news/article-13954609/Sweden-Denmark-ban-marriage-cousins.html)

In the 2nd paragraph of the data subsection of the methods, It is stated that women who did not give full answers to questions about consanguinity were excluded from analysis. How many were

excluded in each set of data? What was the pattern of missingness?

In the introduction, there is a statement that “there were other significant factors associated with” congenital anomalies - what were these, and what was the magnitude of association?

My understanding is that immigrants from Pakistan tended to come from the same geographical area, and then settle in the same area in the UK. This would likely have limited mating choices in a group that strongly encourages family creation in the same culture. Is there any evidence that this has changed between the two periods. Did you collect any information on area of birth? If so, might this be more diverse in the more recent group? Within the study area, do you know if one or both partners had moved from elsewhere in Bradford (or the UK) into the area, and if this differed between the two periods?

References

1. Sweden and Denmark both move to ban marriage between cousins over fears the practice breeds domestic violence. Reference Source

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 13 December 2024

https://doi.org/10.21956/wellcomeopenres.25901.r113710

Parveen Ali
University of Sheffield, Sheffield, UK

Thank you very much for considering and incorporating review.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Inequalities in Health related to gender and ethnicity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 12 December 2024

https://doi.org/10.21956/wellcomeopenres.25901.r113890

Atta Ur Rehman
Hazara University, Mansehra, Khyber Pakhtunkhwa, Pakistan

The authors have compared the prevalence of consanguinity in two independent cohorts (2007-

2010; 2016-2019) from Bradford, England separated by a nine-years gap. Their findings suggest a substantial decline in consanguinity among women of Pakistani heritage over the years. For instance, first-cousin marriages dropped from 39.3% to 27.0%, and other blood relation marriages decreased from 23.1% to 19.3%. Alternatively, the rate of unrelated marriages increased from 37.6% to 53.7% among Pakistani heritage women.

Findings of this study underscore the importance of recognizing shifts in consanguinity rates and associated health needs for planning antenatal, pediatric, and genetic services in Bradford and similar communities. The observed trends may reflect broader changes in partner selection within these populations. In general, the authors have prepared a well-structured manuscript with clear presentation of objectives and results. However, I have a few comments:

Introduction: The authors have reasonably provided basic knowledge about consanguinity, its global prevalence, and correlation of consanguinity with congenital anomalies especially recessive disorders. However, I would suggest the authors to briefly discuss about the recent patterns/trends in consanguinity in native Pakistani population. This will be integral for findings of this study because a recent study [PMID: 38314634] has shown a temporal decline in consanguinity in Pakistan which is quite similar to findings of this study.

Methods: Since consanguinity rates are not uniform across Pakistan and are influenced by many variables, it would be more interesting if the authors could provide data or at least mention about the various sociodemographic attributes of their respondents including ethnicities, language, geographic location etc.

Results: The results are self-explanatory; thus, I suggest no changes.

Discussion: The authors need a more comprehensive discussion on their findings in the context of Pakistani population since the respondents are largely of Pakistani heritage. Also, the authors need to fully appreciate regional differences in consanguinity rates within Pakistani community, especially by identifying regions where highest rates of consanguinity has been reported. The authors need to associate their findings with the recent trends in consanguinity in Pakistan (For details, please refer to: PMID: 38314634).

References

1. Sajid Malik, Anisa Bibi, Rubbiya Farid, Sidra Khan, Javaid Awan, Atta Ur Rehman: Consanguinity in northwest Pakistan: evidence of temporal decline. Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My interest is at the interface between human genetics and epidemiology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 07 November 2024

https://doi.org/10.21956/wellcomeopenres.23363.r107687

Anisa Bibi
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Summary:
This article uses information from two important cohort studies to examine the prevalence and changing trends of consanguineous marriages in Bradford, UK. Marriage between relatives, or consanguinity, is a social phenomena that affects genetic health, especially in communities where consanguinity is more common. By contrasting data from two cohorts gathered at various points in time, the authors hope to provide a thorough examination of consanguinity patterns in Bradford and gauge shifts in prevalence and attitudes.

Given Bradford's distinct demographic profile—which includes a sizable population of South Asian heritage, where consanguinity has long been practiced—the question is quite pertinent. In a healthcare setting where genetic risks related to consanguinity are of concern, the study offers important insights into how cultural practices change over time within immigrant populations.

Title and abstract: The title is appropriate and sums up the primary focus of the research. The abstract clearly conveys the main findings, methodology, and goals of the study and is well-

structured. Clarity would be improved by including a brief overview of the study's limitations.

Introduction: The significance of researching consanguinity in Bradford is clearly stated in the introduction, which also highlights the ramifications for culture and health. It highlights a knowledge gap about the temporal variations in consanguinity prevalence and patterns and gives a good summary of earlier research. The stated goals of the study are well-aligned with the background information. The case for this study might be strengthened, nevertheless, by additional discussion of the possible genetic consequences and public health significance.

Methods:
Cohort studies are suitable for longitudinal studies.

The background information is sufficient, and the cohort, inclusion, and exclusion criteria employed provide accurate representations of the Bradford community. The data collection procedure was suitable. The statistical techniques were appropriate and sufficient. The pattern and data analysis were satisfactory. They talk about the limitations and possible biases in consanguinity data.

Results:
Every cohort study is covered sequentially, and the results are arranged rationally. Key data has been presented by the writers using tables and figures in an efficient manner, and the text well supports them.The authors provide adequate context for readers to grasp the findings' importance, especially when comparing data from two different cohort studies. The results directly address the main objective of the paper—understanding changes in the prevalence and patterns of consanguinity over time.The statistical methods employed to examine the data are suitable for the kind of data generated and the study design. When applicable, the authors report statistical significance and include metrics such as confidence intervals to show how accurate their predictions are. The data was well interpreted. The conclusions about changes in consanguinity patterns justified by the data and author acknowledge the potential biases.

Bradford has a distinct demographic with a significant South Asian community, making it a good place to examine consanguinity patterns because consanguineous marriages are more prevalent there. Understanding the genetic and societal factors that may affect public health and the need for genetic counseling will be improved by the current study.

Discussion and conclusion:
There is a clear fall in first cousin marriage from 39.3% to 27.0% and those who were of other blood relations fell from 23.1% to 19.3%. The study highlighted ethnic disparities, showing that consanguinity remains more common among South Asian communities compared to the general population. However, there was also an observed increase in consanguineous marriages in other ethnic groups over time.

Younger individuals and those with higher educational attainment were less likely to engage in consanguineous marriages, while consanguinity was more common among older generations and those with lower educational levels.

The study stresses the potential public health implications of high consanguinity rates, such as the increased risk of autosomal recessive genetic disorders. It calls for improved genetic counseling

and screening services for affected populations. The research indicates a shift in marriage patterns in the South Asian community, with a higher rate of consanguinity in later generations, possibly influenced by changing social norms and migration patterns.

These findings underscore the complex interplay of cultural, social, and demographic factors influencing consanguinity and its potential health impacts in the context of a multicultural society like Bradford.

Key strengths:
Longitudinal Approach: By comparing two datasets from several eras, the study provides an insightful look at consanguinity trends across time. This method enables trend analysis, which may shed light on the consequences of acculturation, generational changes, and evolving societal norms.

Population Significance: Bradford is a good place to study consanguinity because of its large proportion of people of South Asian heritage. The results could influence community participation tactics, genetic counseling programs, and regional health policy.

Methodological Rigor: The study makes use of strong statistical analyses, such as comparisons of the prevalence of consanguinity and its relationship to sociodemographic variables. The study is more reliable and reproducible because the authors have provided a comprehensive explanation of their methods.

Relevance to Clinical and Public Health: Knowledge of consanguinity prevalence and trends helps identify at-risk populations, and these results can be used directly to enhance risk awareness and genetic counseling in healthcare.

Areas for improvement:

Clarification of Cohort Differences: Despite the fact that two cohorts were examined, a more thorough comparison of the cohorts' sample attributes, recruiting strategies, and potential confounders will enhance the article. The comparability of the datasets and any potential biases in the observed changes over time would be better understood by readers as a result.

Interpretation of Socioeconomic Influences: Although socioeconomic issues are mentioned in the article as having an impact on consanguinity practices, this topic might be further investigated. The analysis might be strengthened by a thorough examination of the ways in which acculturation, income, and educational attainment affect the prevalence of consanguineous marriage.

Consideration of health outcomes: A brief analysis or description of the health outcomes associated with consanguineous unions among the cohorts under study could give more context and highlight the public health concerns, even though the main focus is on prevalence.

Community Perceptions: Qualitative information about how the community views consanguinity would help the article better contextualize the trends. This could clarify whether societal factors, healthcare awareness, or other influences are the main drivers of these transitions and help explain the patterns that have been seen.

Graphical Representation: Trend graphs or demographic analyses of consanguinity trends are two examples of graphics that could better convey some of the findings. Both academic and non-academic readers would find the piece easier to read and more engaging as a result.

Conclusion:
The work addresses a frequently disregarded facet of public health and community health dynamics, making a significant contribution to our understanding of consanguinity in the UK. Although the paper is valuable and well-researched, its depth and impact might be increased by including more in-depth socioeconomic analysis, health outcomes data, and community perspectives.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Human Genetics, Epidemiology, clinical and medical genetics, public health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 26 Nov 2024

Neil Small

We are very grateful for the supportive and insightful comments of our reviewer. We agree with the points that the paper's depth and impact might be increased by including more in-depth socioeconomic analysis, health outcomes data, and community perspectives. We have been working on allied and complimentary studies alongside the study our reviewer's report relates to. When we posted this article, and when it was sent for review, two key pieces of work were still in development. These are now completed and are available to

augment this article.
Small N, Kelly B, Malawsky D S *et al.* Mortality, morbidity and educational outcomes in children of consanguineous parents in the Born in Bradford cohort [version 2; peer reviewed]. *Wellcome Open Res* 2024, 26 Sep 2024a, **9**:319 (https://doi.org/10.12688/wellcomeopenres.22547.2)
Small, N., Razaq, R et al. Changing patterns in marriage choice and related health risk in the Pakistani heritage community in Bradford UK: a qualitative study. Wellcome Open Research 22/11/24 9: 690 https://doi.org/10.12688//wellcomeopenres.23338.1 We have now cited them within this article.

Areas reviewer 2 identified that would improve the article:

Clarification of Cohort Differences: *Despite the fact that two cohorts were examined, a more thorough comparison of the cohorts' sample attributes, recruiting strategies, and potential confounders will enhance the article. The comparability of the datasets and any potential biases in the observed changes over time would be better understood by readers as a result.*

Interpretation of Socioeconomic Influences: *Although socioeconomic issues are mentioned in the article as having an impact on consanguinity practices, this topic might be further investigated. The analysis might be strengthened by a thorough examination of the ways in which acculturation, income, and educational attainment affect the prevalence of consanguineous marriage.*

Re cohort differences and socioeconomic analysis – both our two cohort profiles – cited in the article (Wright et al 2013 and Dickerson et al 2022) and our two cohort protocols (Raynor et al 2008 and Dickerson et al 2016) – and material in our Extended data for this article and in Small et al 2024 give a lot of socioeconomic background and a lot of detail about the process of setting up and undertaking the cohort studies. We agree that further detailed analysis of specific factors would further strengthen our points. We hope to be able to consider such matters via exploration of specific research questions in future work. We also think deep analysis of differences between the cohorts would enhance future work on data from other areas of the cohort studies where comparison would be valuable. This article is, we hope, not the last in which we explore the benefits of cross-cohort comparison.

Consideration of health outcomes: *A brief analysis or description of the health outcomes associated with consanguineous unions among the cohorts under study could give more context and highlight the public health concerns, even though the main focus is on prevalence.*

We have looked at health outcomes – beyond recessive disorders - using data that are available up to age 10 for all children in our cohort. They identify excess mortality and morbidity and also look at impact on educational attainment – see Small et al 2024a. This reference is now cited in the article.

Community Perceptions: *Qualitative information about how the community views consanguinity would help the article better contextualize the trends. This could clarify whether societal factors, healthcare awareness, or other influences are the main drivers of these transitions and help explain the patterns that have been seen.*

We have carried out a qualitative study with members of the Bradford population who are of Pakistani heritage. They helped us explore changing attitudes to consanguinity and to the way health services respond to it – see Small, Razaq et al 2024. This reference is now cited in the article.

Graphical Representation: *Trend graphs or demographic analyses of consanguinity trends are two examples of graphics that could better convey some of the findings. Both academic and non-academic readers would find the piece easier to read and more engaging as a result.*
We agree with this point and will consider these ways of presenting complex data in an accessible way in subsequent studies.

Competing Interests: no competing interests

Reviewer Report 20 June 2024

https://doi.org/10.21956/wellcomeopenres.23363.r83070

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Parveen Ali
[1] University of Sheffield, Sheffield, UK
[2] University of Sheffield, Sheffield, UK

Thank you for submitting this manuscript which is written well and I only have a few questions/ comments/

You mention in the abstract that '*Research undertaken using the Born in Bradford cohort study identified consanguinity as a major risk factor for congenital anomalies and also reported longer term adverse health outcomes associated with consanguinity'.* It is a risk factor but don't think it is a major risk factor

There is not much difference in how scientific abstract and plain English Summary in reported. Plain English summary needs to be more accessible for lay audience.
While consanguinity increases the risk of recessive disorders, at population level the risk is only 6% so not a huge high risk, however, the fact that it is concentrated in affected families and the conditions are severe, it is an important issue. Please clearly articulate this in your introduction to help reader understand context, else it reads as if every consanguineous couple is going to affected by recessive disorder which is not the case.

What are the implications of the study, please state clearly in conclusion

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Inequalities in Health related to gender and ethnicity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Nov 2024

Neil Small

Parveen Ali – Reviewer 1.
Comment One: *You mention in the abstract that 'Research undertaken using the Born in Bradford cohort study identified consanguinity as a major risk factor for congenital anomalies and also reported longer term adverse health outcomes associated with consanguinity'. It is a risk factor but don't think it is a major risk factor*
We are grateful for this comment. We are aware that discussing risk involves complex considerations. Our research has found that consanguinity doubles risk of congenital anomalies and that no other factors (except age of mother – over 34 years) that have been considered in the literature (deprivation/co-morbidities etc) are supported by our data (Sheridan et al 2013). However, the considerable majority of children born to consanguineous parents will not have an anomaly (94%) and anomalies occur randomly in non-consanguineous children (at a rate of about 3%). We appreciate the reviewer's observation that it needs to be clearer that recessive disorders are not evident in the offspring of a considerable majority of consanguineous parents and that this clarity also needs to be present in our Plain Language Summary. We have added the following paragraph to our Introduction: Congenital anomalies occur in all communities. Rates are higher in children born to consanguineous parents although even here the considerable majority of children will not have an anomaly. In the BiB study about 3 in every 100 children born to non-consanguineous parents and about 6 in every 100 born to consanguineous partners were born with an anomaly. There are also other significant factors associated with increased presence of congenital anomalies. BiB reported an increase in risk of similar magnitude to consanguinity for non-consanguineous mothers of white British origin older than 34 years. Further, anomalies of different sorts and with risk factors other than consanguinity occur in all babies (Sheridan et al. 201**3**). But even though congenital anomalies occur in only a small proportion of children, the consequences of being born with

one can be severe (Small et al 2024a). These consequences include the death of the child or long term morbidity. Given that there are high numbers of consanguineous parents in Bradford, and despite most of their children not having a congenital anomaly, the numbers dying or living with the consequences of a congenital anomaly in Bradford are significant to the city and to its health services.

Comment Two: *There is not much difference in how scientific abstract and plain English Summary in reported. Plain English summary needs to be more accessible for lay audience. While consanguinity increases the risk of recessive disorders, at population level the risk is only 6% so not a huge high risk, however, the fact that it is concentrated in affected families and the conditions are severe, it is an important issue. Please clearly articulate this in your introduction to help reader understand context, else it reads as if every consanguineous couple is going to affected by recessive disorder which is not the case.*
See responses to comment One re being clearer on the nature of risk. In addition to the changes made in responses to comment one we have also rewritten our Plain Language Summary (pls) – our reviewer correctly points out that it closely replicated our Abstract – the new version does not do that, it makes a prominent point that a considerable majority of children born to consanguineous parents will not have an anomaly and it accords more closely with Wellcome Open guidance on requirements for the pls. New Plain language summary Born in Bradford (BiB) studies health and well-being of children in this north of England city. Of interest has been the impact that parents who are blood relations (most often cousins) have on their children's health. These unions increase the risk of one sort of genetic disorder, recessive genetic disorder. While the considerable majority of children born to cousins will not have these disorders the numbers who do are higher than in children of non-blood related parents. These disorders can have a severe impact. Cousin marriages are rare in the UK but are common in some communities, including the Pakistani heritage community in Bradford. Sixty-five percent of mothers recruited to BiB were of Pakistani heritage and 62% of these were married to cousins. BiB recruited women between 2007 and 2010. A second cohort of mothers were recruited between 2016 and 2019 (the Born in Bradford Better Start Study, BiBBS.) BiBBS also had a majority of women who were of Pakistani heritage. Over a nine year period there had been a reduction in the proportion of cousin marriages. Forty-six per-cent of Pakistani heritage women were related to the father of their baby in BiBBS. The reduction was most marked in women who were born in the UK, in those educated to A level or higher and in those under age 25. Comparing cohorts across time is a valuable way to examine social change. A reduction in cousin marriage is likely to reduce the number of recessive genetic disorders and be a positive contribution to the health of Bradford's children. This study is from one city. Changes in Bradford may be attributable to local factors; partner choice may be different elsewhere. But if they indicate a wider trend in Pakistani heritage communities then they could have widespread relevance.

Comment three: *What are the implications of the study, please state clearly in conclusion*
We have expanded our conclusions to try and make clearer our key implications. In addition, implications are considered in our sections "Two cohort analysis" re methodological strengths of undertaking cohort studies with similar populations but with recruitment separated by a number of years. We also discuss how reasons for the behavioural changes we report can be explored qualitatively in our section on "Reasons for

reductions in consanguinity" and we can now reference the qualitative study that complements this study and was not available when we first posted this paper – see Small, Razaq et al 2024. This modified paragraph now reads: Our data suggests some key areas to be explored but, in itself, does not explain why there has been a reduction. We have carried out qualitative research to explore reasons why members of the Pakistani heritage community in the city think rates of consanguinity might have changed over time. This qualitative research considers involvement in education, changes in migration patterns and differences in partner choices depending on age of women alongside other factors that were raised by our participants. We also looked at more distal factors including changes in economic wellbeing and shifts in the law and regulations shaping migration to the UK (Small, Razaq et al 2024). The main implication, described in our conclusion is that a drop in consanguinity in Bradford is likely to reduce the numbers of recessive disorders in children and also to reduce the higher mortality and morbidity we have shown to be associated with consanguinity, findings that have now been published and that we can now cite in this study (Small et al 2024a). We make the point that changes in Bradford may be attributable to local factors but if they indicate a wider trend in Pakistani heritage communities then they could have widespread relevance. Drops in rates of consanguinity are greatest in younger women, those under age 25 at the birth of their first child. Staying longer in education and being born in the UK are also linked to lower rates of consanguinity. This social change affects genetic health in individuals and, in communities where consanguinity is common, it has wider planning and service provision implication. We have added the following to our conclusion: Knowledge of consanguinity prevalence and trends, and the detailed characteristics of who is in consanguineous unions, helps identify at-risk populations, and this can be used to enhance risk awareness and to help target genetic counselling. The identification of the reductions in consanguinity we report, in particular the considerable reductions in younger people, underscore a complex interplay of cultural, social, and demographic factors. It may be that we are seeing generational changes, and newly evolving societal norms. But these changes need to be monitored to see if they are indications of a lasting change and they need to be considered in other settings where consanguinity is common to see how widespread these reductions in consanguinity are. These are the two additional articles that are linked with this article and were not available when this article was published and sent for review. These are now cited.

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Small N, Kelly B, Malawsky D S *et al.* Mortality, morbidity and educational outcomes in children of consanguineous parents in the Born in Bradford cohort [version 2; peer reviewed]. *Wellcome Open Res* 2024, 26 Sep 2024, **9**:319 (https://doi.org/10.12688/wellcomeopenres.22547.2) Small, N., Razaq, R et al 2024. Changing patterns in marriage choice and related health risk in the Pakistani heritage community in Bradford UK: a qualitative study. Wellcome Open Research 22/11/2024 9:690 https://doi.org/10.12688//wellcomeopenres.23338.1

Competing Interests: no competing interests