Might infection explain South Asians' higher coronary heart disease risk?: systematic review comparing prevalence rates with White populations in developed countries

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ABSTRACT

Objectives: South Asians in developed countries like the United Kingdom have comparatively high coronary heart disease risk, for reasons which are not fully understood. One unexplored hypothesis is more infections in this ethnic group. We assessed whether prevalence of infections among South Asians differs from European origin, White populations in developed countries.

Study design: Systematic review.

Methods: A systematic literature review was carried out using Medline, Web of Science and Google Scholar databases. Reference lists and citations were reviewed.

Results: 21 studies reported prevalence rates and mean antibody levels of infection with 17 different pathogens or non-specific markers of infection. Among bacterial infections, we found higher rates in South Asians for *Escherichia coli* and *Mycobacterium tuberculosis*. No consistent differences were found for periodontal pathogens, *Helicobacter pylori, Staphylococcus aureus, Chlamydia pneumoniae* and *Mycobacterium avium*. For viral pathogens, higher rates in South Asians were found for hepatitis A, hepatitis B, and cytomegalovirus, lower rates for herpes simplex, hepatitis C, human immunodeficiency virus and varicella zoster virus, and no difference for hepatitis G virus. Levels of non-specific markers of infection (total immunoglobulin G, endotoxin) were higher in South Asians.

Conclusions: The number of studies was small. We found differences in specific infections, but the current evidence is insufficient to support or reject the hypothesis under examination. Further studies are warranted.

Keywords: infectious burden, ethnicity, South Asian, coronary heart disease

INTRODUCTION

South Asians − people with ancestral origins in the Indian subcontinent countries of India, Pakistan, Bangladesh, Sri Lanka − living in developed countries with White European majority populations tend to have a comparatively high mortality risk of coronary heart disease (CHD).[1-8] Despite considerable research the explanation for this phenomena is not completely determined. Although the role of conventional risk factors for atherosclerosis − such as tobacco smoking, diabetes mellitus, hyperlipidaemia, hypertension − and the potential complex interaction between them - is well recognised, currently these do not fully account for the increased risk among South Asians.[9-11] Large-scale cohort studies are required to assess interactions. Although such studies are currently in progress,[12] to date no longitudinal data are available in the European setting, specifically for South Asian populations.[13]

Novel atherogenic markers have emerged in recent years including chronic systemic infections.[14,15] The relation between infection and atherosclerosis has been of compelling interest but is unclear. In the last decade the most intensively investigated infection has been *Chlamydia pneumoniae* but *Helicobacter pylori,* cytomegalovirus (CMV), herpes simplex virus (HSV), *Mycobacterium tuberculosis,* influenza and periodontal infections have also emerged in this context.[14,16-21] A focus on individual infective agents has not yielded conclusive results leading to the hypothesis that atherosclerosis might not be specific to one organism but to the aggregate “pathogen burden”.[22] Several studies have supported this hypothesis,[23-25] although others did not.[26,27] Systemic infections could potentially impact on the atherosclerotic process in various ways. Microbes could alter endothelial cell function and injure the vessel wall directly, or the infection-induced inflammatory response could have pro-atherosclerotic effects through elevated levels of acute phase proteins or through an autoimmune mechanism called molecular mimicry.[23,24,28] Increased serum level of C-reactive protein (CRP) was specifically suggested as an important risk factor for CHD in South

Asians.[29] However, a recently published mendelian randomisation study did not support this hypothesis.[30]

The pattern of infection in South Asians compared to White European populations has not yet been systematically reviewed. Our purpose was to review the literature to see whether systemic infections were more common among populations of South Asian ethnic origin than among majority ethnic populations in developed countries. The objective was to assess whether the infection hypothesis was a serious contender, among the many explanations offered by Bhopal,[31] in explaining the comparatively high CHD rates in South Asians.

METHODS

Search strategy

Using the search terms and strategy described in the Appendix 1, Medline, Google Scholar and Web of Science database were searched from inception to April 2011. Reference lists were studied for additional papers. Personal bibliographic databases of Professor RS Bhopal and Dr C Fischbacher were also searched.

Inclusion and exclusion criteria, study selection

We included original, quantitative, epidemiological studies which described participants with ancestral origins in the countries that are now India, Pakistan, Bangladesh and Sri Lanka and living in developed countries including countries of the European region, United States, Canada, Australia, New Zealand and South Africa. We included only studies that provided comparisons with "White Europeans" or the "general population" and which reported quantitative measures of markers of systemic infections, focussing on specific infections previously associated with CHD, including *C. pneumoniae*, CMV, *H. pylori*, HSV, *M.*

tuberculosis, P. gingivalis, influenza or providing measures of total levels of non-specific markers of infection such as IgG, total IgA or total IgM. Only English language papers were reviewed.

We excluded studies that examined "Asian" populations without evidence that they were of Indian subcontinent origin. We also excluded studies that reported local infections with low potential to contributing a generalised atherosclerotic process, such as vulvitis caused by *Chlamydia trachomatis*, urethritis caused by *Neisseria gonorrhoeae* or bacteruria.

Statistical analysis of the retrieved data

If statistical analysis was not performed or results were not reported in the study, we calculated confidence intervals for proportions and calculated prevalence rate ratios from the available data, using Epi Info 3.5.1 software (Centers for Disease Control and Prevention, Atlanta, US). Such calculations were marked on the tables with a dagger symbol. As statistical power of some studies was low due to small sample size, we have distinguished those results where the difference between the two ethnic groups was not statistically significant but was equal to or higher than 20%, a difference that we judged as potentially important and needs larger studies.

Table 1.

RESULTS

Methods of reviewed studies

Twenty-one studies met the inclusion criteria.[32-52] Table 1 shows the main features of the studies identified. They are categorised according to the infectious agents or markers of infection examined and the date of publication. All studies were cross-sectional or reported cross-sectional data from case control or cohort designs. Most studies were in the United

Kingdom, but we identified papers from Australia,[39] South Africa,[42] the United States,[46] Italy,[47] and New Zealand.[50] Only four studies examined randomly selected general population samples.[36,37,51,52] Other studies were based on schoolchildren,[33,34,39,40,44] three-year-old children[50] or neonates;[48] lactating or pregnant women;[32,41,45,46,49] hospital patients or clinic attendees;[35,38,42,43] and volunteers from specific groups like blood donors, immigrants, haemodialysis patients or drug users.[42,47] Five studies included only women,[32,41,45,46,49] one only men[43] and 10 both genders,[35-39,44,47,50-52] while five did not give gender.[33,34,39,42,48] The indicator of ethnicity was stated in only 13 studies, mostly self reported ethnicity[37,38,41,43,45,50,51] or country of birth or parents' country of birth,[39,47-49,52] or both.[44] Sample size mostly varied from 44 to 1910 for White Europeans and from 9 to 1274 for South Asians, excepting one study[48] of 340573 blood samples from White European donors and 45471 samples from South Asians.

Table 2.

Results of reviewed studies

Table 2 shows there were 15 pathogens studied: seven bacterial[32-40] and eight viral agents.[41-50] Two non-specific infectious disease markers were investigated.[51,52] Mostly, exposure to infection was detected by measuring IgG, IgM or IgA type antibodies with ELISA in blood samples, but also IgA antibodies in breast milk;[32] IgG in oral fluid samples;[44] skin tests;[39,40] identification of pathogens in saliva samples,[33] subgingival plaque samples[34] or gastric biopsies;[35] endotoxin measurement in blood samples[52] were used. Ten studies adjusted the outcome results for potential confounding factors.[33,36-38,40,41,46,50-52] In all the adjusted studies sex and age were taken into account; four studies also adjusted the results for social status,[36,37,41,50] and three for cardiovascular risk factors like smoking or blood lipid levels.[38,51,52] Outcome measures were usually the proportion of participants positive for the examined infection. Only three studies gave average levels of antibody or antigen concentration.[37,51,52] In one study the mean pathogen (*Escherichia coli*) specific antibody level was compared to the mean total non-specific antibody level.[32]

Bacterial infections: Among the seven bacterial pathogens investigated only *E. coli*[32] and *M. tuberculosis*[39,40] were consistently more common in South Asians. The difference was statistically significant for *E. coli* and partly significant for *M. tuberculosis.* The difference between the two ethnic groups was negligible (smaller than 20% and showed no statistical significance) for *C. pneumonia*[38] and *Mycobacterium avium.*[40] Results were mixed for infections with periodontal pathogens,[33,34] *H. Pylori,*[35-37] and *Staphylococcus aureus:*[37] for periodontal pathogens one study found no difference,[33] the other found a significantly higher rate in South Asians;[34] three studies that compared *H. pylori* infection gave conflicting results: no difference,[36] statistically not significant but higher rates in South Asians,[35] statistically significant lower rates in South Asian females;[37] higher antibody levels against *S. aureus* toxin A and toxin B were reported in South Asians but no such difference was seen for toxin C and for TSST-1.[37]

Viral infections: Eight viral pathogens were investigated from which hepatitis A virus (HAV),[42-44] hepatitis B virus (HBV),[45,46] and CMV[50] were more common in South Asians. The difference was statistically significant for CMV and HBV but was not consistently significant for HAV. HSV,[41] hepatitis C virus (HCV),[45] human immunodeficiency virus (HIV)[48] and varicella zoster virus (VZV)[49] turned out to be less common in this ethnic group. Except the one for HCV, all results were statistically significant. Hepatitis G virus (HGV)[47] showed no difference between the two ethnic groups.

Non-specific markers of infection: Both total IgG level[51] and endotoxin level[52] showed higher mean levels in South Asians. The differences were statistically significant except when the comparison between endotoxin levels were adjusted with metabolic risk factors like blood levels of insulin, HDL or triglyceride.

Overall: From the 17 specific pathogens and non-specific markers of infection seven found to be more common in South Asians (*E. coli,*[32] *M. tuberculosis*,[39,40] HAV,[42-44] HBV,[45,46] CMV,[50] total IgG level,[51] endotoxin level[52]). The difference was statistically significant in four (*E. coli,*[32] HBV,[45,46] CMV,[50] total IgG level[51]). Four pathogens were less common in South Asians (three statistically significant differences: HSV,[41] HIV,[48] VZV[49] and one not significant: HCV[45]). Three pathogens showed no difference (*C. Pneumonia,*[38] *M. avium,*[40] HGV[47]), and three gave mixed results (periodontal pathogens,[33,34] *H. pylori,*[35-37], *S. aureus*[37]).

DISCUSSION

Overview of key findings

Overall, this review indicates differences for certain specific infections between South Asians and White Europeans in developed countries. Among the pathogens associated with atherosclerosis there was consistent evidence that *M. tuberculosis* and CMV infection were more common in South Asians.[39,40,50] However, HSV was less common in this ethnic group.[41] There was no consistent evidence of differences in the prevalence of infection with *C. pneumoniae, H. pylori,* or periodontal pathogen infections.[33-38] Among infectious agents or infectious markers that have not been previously linked with CHD, *E. coli*, HAV, HBV, total IgG and endotoxin level were more common,[32,42,43-46,51] and HIV, VZV and HCV less common in South Asians.[45,48,49] For a further three pathogens clear ethnic differences were not found.

Limitations and strengths

We found only five pathogens that were investigated by more than one study (periodontal pathogens,[33,34] *H. pylori,*[35-37] *M. tuberculosis,*[39,40] HAV,[42-44] HBV[45,46]) and for the other 12 infectious agents or markers of infection one single study was found for each. This, as well as the significant heterogeneity in study populations, differences in indicator of infection and often low sample size, made the interpretation difficult. Recent studies have confirmed the inverse association between infectious burden and socioeconomic and educational status.[53,54] Furthermore the greater pathogen burden in developing countries is well known. These findings make it necessary to take into account social class, educational level and the time that a person spent in developing countries when interpreting data.

We found only four studies[37,38,41,51] which had relatively high participation rate (i.e.: more than 100 subjects in each ethnic groups) and also adjusted the results for social class and/or cardiovascular risk factors. However, even if the analysis is restricted to these higher quality studies, the differences between the two ethnic groups in overall infectious rates remained inconsistent. (*H. pylori, S. aureus* giving mixed results;[37] *C. pneumonia* showing no difference;[38] HSV showing lower rate in South Asians;[41] and total IgG showing higher rates in South Asians[51])

We summarised the differences in individual infectious rates between South Asians and White Europeans. Evidence on the cumulative pathogen burden was limited as studies examined only one or two pathogens. Hence, only the two studies that reported data on non-specific markers of infection[51,52] measured, indirectly, some levels of actual cumulative pathogen burden.

Conclusion

Our systematic review provided evidence of ethnic differences in some specific infections, but no clear support for the overall burden of infection hypothesis. From the individual pathogens which might contribute to the evolution of atherosclerosis *M. tuberculosis* and CMV were reported to be more common in South Asians. The small number and methodological weaknesses of the relevant studies limit our conclusions. Further studies with appropriate control of potential confounders are needed to clarify the role of these specific pathogens.

To pursue the question we would need to measure prevalence rates of all the potentially relevant pathogens in representative population samples in each of the ethnic groups of interest. Such research has been already carried out on other ethnic groups,[55] and a study of South Asians is required. A multi-ethnic cohort study with repeatedly collected data on pathogen burden would provide even stronger evidence. Until these studies are done, the question posed by the systematic review remains open.

More sound understanding of the factors which contribute to the high CHD risk of South Asians would allow more specific and focused public health interventions in this ethnic group. If infection plays a role, it imposes a double disease burden on affected individuals and preventive measures would be particularly important. In light of these, the answer for the question could have relevant public health implications in the future.

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Ethical approval: Not required

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Table 1.: Contextual details of the studies on bacterial infections (A), viral infections (B) and non-specific markers of infection (C): publication, time and location of the study, sample selection, sex and age distribution of study populations, sample size

A. Bacterial infections

Study *(First author, date of publication, examined pathogen or indicator of infection, reference)*	***a.Date of fieldwork, b.Place, c.Basis of sample***	***% females***	***Mean age in years***	***Inclusion criteria***	***Indicator of ethnicity***	***Response rate***	***Sample size***
Nathavitharana KA, 1994 *Escherichia coli* [32]	a.Not stated b.Birmingham, UK c.Volunteer lactating women	100%	W: 29 (r: 20-39) SA: 26 (r: 20-37)	Lactating women	Not stated	Not stated	W: 75 SA: 20
Drucker DB, 1995 Periodontal pathogens [33]	a.Not stated b.Keighley, UK c.Targeted sample of schoolchildren	Not specified	5	Children who had teeth with obvious carious lesions	Not stated	Not stated	W: 70 SA: 70
Elwood R, 1997 Periodontal pathogens [34]	a.Not stated b.Manchester, UK c.Targeted sample of schoolchildren	Not specified	13 (SD: 0.33)	Children had to have both upper first permanent molars present, no history of rheumatic fever, jaundice, hepatitis, heart disease or be taking antibiotics	Not stated	Not stated	W: 333 SA: 187
Seery JP, 1997 *Helicobacter pylori* [35]	a.Not stated b.Southall, UK c.Consecutive hospital patients	W: 41% SA: 46%	W: 47 SA: 45	Not stated	Not stated	Not stated	W: 107 SA: 124
Stone MA, 1998 *Helicobacter pylori* [36]	a.Not stated b.Leicester, UK c.Randomly selected subjects in one GP district	W: 56% SA: 54%	W: 44 SA: 40	People between 21-55 years	Not stated	W: 22.6% SA: 28%	W: 44 SA: 112
Fischbacher CM, 2004 *Helicobacter pylori, Staphylococcus aureus* [37]	a.W: Apr 1993 – Oct 1994 SA: May 1995 – March 1997 b.Newcastle upon Tyne, UK c.Randomly selected subjects from the Newcastle Heart Project (NHP)	W: 52% SA: 54%	W: 54 (SD: 13) SA: 50 (SD: 12)	People between 25-74 years	Self reporting: W: ancestral origin in Europe SA: 3 or more grand parents from the Indian Subcontinent	NHP: W: 67.5% SA: 64.2%	W: 302 SA: 300

Continued

Study *(First author, date of publication, examined pathogen or indicator of infection, reference)*	***a.Date of fieldwork, b.Place, c.Basis of sample***	***% females***	***Mean age in years***	***Inclusion criteria***	***Indicator of ethnicity***	***Response rate***	***Sample size***
Cook PJ, 1998 *Chlamydia pneumoniae* [38]	a. Jan 1993 – Jan 1995 b.Birmingham, UK c.Randomly selected hospital patients	W: 43% SA: 48%	W: 60 (SD: 17.4) SA: 49 (SD: 17.3)	No evidence of active cardiac, vascular, pulmonary disease; No known/suspected immuno-deficiency, autoimmun disease, hyper-gammaglobulinaemia	Self reporting	96%	W:1061 SA: 290
Johnson PDR, 1998 *Mycobacterium tuberculosis* [39]	a. 1995 b.Melbourne, Australia c.Partly random and partly targeted sample of schoolchildren	Not specified	r: 9-10	Not stated	Country of birth	49%	W: 156 SA: 114
Weir RE, 2003 *Mycobacterium tuberculosis, Mycobacterium avium* [40]	a.Feb 1999 – Apr 2000 b.Southeast England, UK c.Volunteer schoolchildren	49%	13 (r: 12-15)	No record of BCG vaccination or any serious or immunmodulatory disease	Not stated	Not stated	W: 321 SA: 32

B. Viral infections

Ades AE, 1989 Herpes Simplex Virus (HSV) [41]	a.1980–1981 b.London, UK c.Consecutive pregnant women attending antenatal clinics	100%	Not specified	Not stated	Self identification	Not stated	W:1226 SA: 742
Sathar MA, 1994 Hepatitis A Virus (HAV) [42]	a.Not stated b.Durban, South Africa c.Randomly selected hospital patients, outpatient attendees, volunteer blood donors	Not specified	W: r: 17-87 SA: r: 17-84	Not stated	Not stated	Not stated	W: 187 SA: 163
Ross JDC, 2002 Hepatitis A Virus (HAV) [43]	a.Not stated b.Birmingham, UK c.Consecutive outpatient facility attendees	0%	Not specified	Age over 16 years, not received normal immun-globulin in the last 12 months, not vaccinated against HAV, not infected with HIV	Self identification	Not stated	W: 146 SA: 9

Continued

Study *(First author, date of publication, examined pathogen or indicator of infection, reference)*	***a.Date of fieldwork, b.Place, c.Basis of sample***	***% females***	***Mean age in years***	***Inclusion criteria***	***Indicator of ethnicity***	***Response rate***	***Sample size***
Morris-Cunnington M, 2004 Hepatitis A Virus (HAV) [44]	a.Not stated b.Northwestern England, UK c.Volunteer schoolchildren	52%	R: 7-12	Not stated	Self identification of parent / Participant's country of birth / Parents' country of birth	20.9%	W: 74 SA: 153
Boxall E, 1994 Hepatitis B Virus (HBV) Hepatitis C Virus (HCV) [45]	a.Not stated b.Birmingham, UK c.Consecutive pregnant women attending an antenatal clinic	100%	Not specified	Not stated	Self identification	Not stated	W:1604 SA:1274
Euler GL, 2003 Hepatitis B Virus (HBV) [46]	a.1990–1993 b.Four states (CT, GA, MI, TX) in the US c.Randomly selected pregnant Women	100%	Not specified	Not stated	Self identification	Not stated	W:1910 SA: 366
Villari P, 2001 Hepatitis G Virus (HGV) [47]	a.1998 b.Lazio, Italy c.Volunteer blood donors, drug users, hemodialysis patients, immigrants	W: 18% SA: Not stated	Not specified	Not stated	Country of origin	Not stated	W: 357 SA: 79
Cortina-Borja M, 2004 Human Immuno-deficiency Virus (HIV) [48]	a.1998–2002 b.London, UK c.Neonatal babies	Not specified	Not specified	Not stated	Place of mother's birth	Not stated	W:340,573 SA: 45,471
Talukder YS, 2007 Varicella Zooster Virus (VZV) [49]	a. Oct 2001 – March 2002 Sept 2003 – Febr 2004 b.London, UK c.Consecutive pregnant women attending an antenatal clinic	100%	W: 28 (SD: 6.4) SA: 26 (SD: 5)	Only British and Bangladeshi women were included	Place of birth / Place of parents' birth	92%	W: 275 SA: 765
O'Brien TP, 2009 Cytomegalo-virus (CMV) [50]	a.Apr 1998 – May 2001 b.Auckland, New Zealand c.Randomly selected children from Auckland Birthweight Collaborative Study (ABCS)	51%	3.5	All babies were born at 37 or more completed weeks of gestation	Self reported by the mother	W: 63.2% SA: 29%	W: 409 SA: 29

Continued

Study *(First author, date of publication, examined pathogen or indicator of infection, reference)*	***a.Date of fieldwork, b.Place, c.Basis of sample***	***% females***	***Mean age in years***	***Inclusion criteria***	***Indicator of ethnicity***	***Response rate***	***Sample size***
C. Non-specific markers of infection							
Fischbacher CM, 2003 Total IgG level [51]	a. W: Apr 1993 – Oct 1994 SA: May 1995 – March 1997 b.Newcastle upon Tyne,UK c.Randomly selected subjects from the Newcastle Heart Project (NHP)	W: 52% SA: 54%	W: 54 (SD: 13) SA: 50 (SD: 12)	People between 25-74 years	Self reporting: W:ancestral origin in Europe SA:3 or more grand parents were born in the Indian Subcontinent	NHP: W: 67.5% SA: 64.2%	W: 302 SA: 300
Miller MA, 2009 Endotoxin level [52]	a. 1994 – 1996 b.London,UK c.Randomly selected subjects from the Wandsworth Heart and Stroke Study (WHSS)	W: 49% SA: 52%	Not specified	age 40-59; no antihypertensive or lipid lowering medication; no oral anticoncipient or hormone replacement therapy; no diabetes; no previous CHD or stroke	WHSS: Subject's and their parent's place of birth	WHSS: 64%	W: 61 SA: 63

W, White European; SA, South Asian
r, Range; SD, Standard Deviation
CT, Connecticut; GA, Georgia; MI, Michigan; TX, Texas
NHP, Newcastle Heart Project; ABCS, Auckland Birthweight Collaborative Study; WHSS, Wandsworth Heart and Stroke Study

Table 2.: Findings and analysis of the studies on bacterial infections (A), viral infections (B) and non-specific markers of infection (C): compared indicator of infection, adjustment, percentage of positive cases or means of antibody levels in study populations, statistical analysis and overall summary of the results († indicates additional analysis by authors)

A. Bacterial infections

Study	*Compared indicator of infection*	*Adjustment*	*Percentage of positive cases (%) or means of antibody levels (m) in study populations (95% CI)*	*Statistical analysis*	*Summary* Infectious rate in South Asians vs. White Europeans
Nathavitharana KA et al. (1994) [32]	***Escherichia coli:*** Mean *E. coli* specific secretory IgA level in breast milk (as a percentage of total non-specific secretory IgA level)	None	(m) W: 0.7 SA: 4.0	$p<0.001$	**Higher** Statistically significant Difference ≥20%
Drucker DB et al. (1995) [33]	***Streptococcus mutans:*** Proportion of cases with over 10^3cfu counts/ml (in saliva samples)	Age, sex, number of unrestored decayed dental surfaces	(%) W: 85.7 (77.5-93.9) † SA: 90.0 (83.0-97.0) †	PRR=1.05 (0.93-1.17) †	**No difference** Statistically not significant Difference <20%
	Lactobacillus: Proportion of cases with over 10^3cfu counts/ml (in saliva samples)	Age, sex, number of unrestored decayed dental surfaces	(%) W: 51.4 (39.7-63.1) † SA: 50.0 (38.3-61.7) †	PRR=0.97 (0.70-1.35) †	**No difference** Statistically not significant Difference <20%
Elwood R et al. (1997) [34]	**Periodontal pathogens:** Proportion of cases with detected pathogens (in subgingival plaques)	None	(%) W: 9.0 (5.9-12.1) † SA: 22.4 (16.5-28.4) †	PRR=2.49 (1.63-3.80) †	**Higher** Statistically significant Difference ≥20%
Seery JP et al. (1997) [35]	***Helicobacter pylori:*** Proportion of positive cases (in gastric biopsies)	None	(%) W: 43.0 (33.6-52.4) † SA: 52.0 (43.2-60.7) †	PRR=1.20 (0.91-1.59) †	**Higher** Statistically not significant Difference ≥20%
Stone MA et al. (1998) [36]	***Helicobacter pylori:*** Proportion of seropositive cases	Age, sex, social class	(%) W: 47.0 (32.3-61.8) † SA: 53.0 (43.8-62.2) †	PRR=0.83 (0.56-1.19) †	**No difference** Statistically not significant Difference <20%
Fischbacher CM et al. (2004) [37]	***Helicobacter pylori:*** Mean IgG level in blood samples (µg/ml)	Age, social class, income, education	men (m) W: 16.7 (13.9-20.2) SA: 11.6 (9.8-13.7)	OR=0.73 (0.55-0.96)	**Lower** Statistically significant Difference ≥20%
			women (m) W: 11.3 (9.4-13.5) SA: 14.3 (12.1-16.9)	OR=1.23 (0.89-1.70)	**Higher** Statistically not significant Difference ≥20%

Continued

Study	*Compared indicator of infection*	*Adjustment*	*Percentage of positive cases (%) or means of antibody levels (m) in study populations (95% CI)*	*Statistical analysis*	*Summary* Infectious rate in South Asians vs. White Europeans
Fischbacher CM et al. (2004) [37] (cont.)	***Staphylococcus aureus:*** Mean IgG level against toxin A in blood samples (µg/ml)	None	men (m) W: 3.6 (3.2-4.2) SA: 5.5 (5.6-6.7)	$p<0.05$ †	**Higher** Statistically significant Difference ≥20%
			women (m) W: 3.4 (3.0-3.9) SA: 4.8 (4.1-5.7)	$p<0.05$ †	**Higher** Statistically significant Difference ≥20%
	Staphylococcus aureus: Mean IgG level against toxin B in blood samples (µg/ml)	None	men (m) W: 10.6 (9.1-12.3) SA: 22.9 (19.0-27.5)	$p<0.05$ †	**Higher** Statistically significant Difference ≥20%
			women (m) W: 12.4 (10.8-14.2) SA: 19.8 (16.7-23.4)	$p<0.05$ †	**Higher** Statistically significant Difference ≥20%
	Staphylococcus aureus: Mean IgG level against toxin C in blood samples (µg/ml)	None	men (m) W: 19.6 (16.8-23.0) SA: 27.0 (22.9-31.7)	$p>0.05$ †	**Higher** Statistically not significant Difference ≥20%
			women (m) W: 22.3 (19.5-25.7) SA: 23.6 (20.2-27.7)	$p>0.05$ †	**No difference** Statistically not significant Difference <20%
	Staphylococcus aureus: Mean IgG level against TSST-1 in blood samples (µg/ml)	None	men (m) W: 8.8 (7.6-10.1) SA: 9.2 (7.7-10.9)	$p>0.05$ †	**No difference** Statistically not significant Difference <20%
			women (m) W: 10.1 (8.8-11.5) SA: 9.0 (7.8-10.5)	$p>0.05$ †	**No difference** Statistically not significant Difference <20%
Cook PJ et al. (1998) [38]	***Chlamydia pneumoniae:*** Proportion of seropositive cases	Age, sex, smoking habit, date of admission	(%) W: 16.6 (14.4-18.8) † SA: 18.9 (14.5-23.5) †	PRR=1.14 (0.88-1.52) †	**No difference** Statistically not significant Difference <20%
Johnson PDR et al. (1998) [39]	***Mycobacterium tuberculosis:*** Proportion of cases with positive Mantoux tests	None	(%) W: 0.6 (-0.6-1.9) † SA: 2.7 (-0.3-5.6) †	PRR=4.10 (0.59-28.59) †	**Higher** Statistically not significant Difference ≥20%

Continued

Study	*Compared indicator of infection*	*Adjustment*	*Percentage of positive cases (%) or means of antibody levels (m) in study populations (95% CI)*	*Statistical analysis*	*Summary* Infectious rate in South Asians vs. White Europeans
Weir RE et al. (2003) [40]	***Mycobacterium tuberculosis:*** Proportion of participants with a positive tuberculin test	Age, sex, attended school	(%) W: 16.0 (12.0-20.0) † SA: 41.0 (24.0-58.0) †	PRR=2.56 (1.52-3.93) †	**Higher** Statistically significant Difference ≥20%
	Mycobacterium tuberculosis: Proportion of participants with positive in vitro IFNγ response to PPD	Age, sex, attended school	(%) W: 22.0 (17.5-26.5) † SA: 47.0 (29.7-64.9) †	PRR=2.12 (1.34-3.04) †	**Higher** Statistically significant Difference ≥20%
	Mycobacterium avium: Proportion of participants with positive in vitro IFNγ response to PPD	Age, sex, attended school	(%) W: 59.0 (53.6-64.4) † SA: 58.0 (40.9-75.1) †	PRR=1.01 (0.71-1.29) †	**No difference** Statistically not significant Difference <20%
B. Viral infections					
Ades AE et al (1989) [41]	**Herpes Simplex Virus** (HSV-1): Proportion of seropositive cases	Age, marital status, social class	(%) W: 80.1 (77.9-82.3) † SA: 72.5 (69.3-75.7) †	PRR=0.91 (0.86-0.96) †	**Lower** Statistically significant Difference <20%
	Herpes Simplex Virus (HSV-2): Proportion of seropositive cases	Age, marital status, social class	(%) W: 7.2 (5.7-8.6) † SA: 3.4 (2.1-4.7) †	PRR=0.47 (0.30-0.72) †	**Lower** Statistically significant Difference ≥20%
Sathar MA et al. (1994) [42]	**Hepatitis A Virus** (HAV): Proportion of seropositive cases	None	(%) W: 50.0 (42.8-57.2) † SA: 67.0 (59.8-74.2) †	PRR=1.33 (1.11-1.58) †	**Higher** Statistically significant Difference ≥20%
Ross JDC, et al. (2002) [43]	**Hepatitis A Virus** (HAV): Proportion of seropositive cases	None	(%) W: 21.0 (14.4-27.6) † SA: 56.0 (23.6-88.4) †	PRR=2.62 (1.19-4.10) †	**Higher** Statistically significant Difference ≥20%
Morris-Cunnington M, et al. (2004) [44]	**Hepatitis A Virus** (HAV): Proportion of seropositive cases (from oral fluid samples)	None; Indicator of ethnicity: parental self identification	(%) W: 13.2 (5.0-21.3) SA: 21.3 (14.8-27.7)	PRR=1.60 (0.86-3.08) †	**Higher** Statistically not significant Difference ≥20%
		Indicator of ethnicity: subject's country of birth	(%) W: 17.3 (12.2-22.5) SA: 54.1 (23.3-84.9)	PRR=3.09 (1.92-5.20) †	**Higher** Statistically significant Difference ≥20%
		Indicator of ethnicity: mother's country of birth	(%) W: 14.3 (7.0-21.7) SA: 22.8 (15.5-30.2)	PRR=1.54 (0.85-2.88) †	**Higher** Statistically not significant Difference ≥20%
		Indicator of ethnicity: father's country of birth	(%) W: 13.7 (5.7-21.7) SA: 21.8 (15.0-28.5)	PRR=1.60 (0.86-3.08) †	**Higher** Statistically not significant Difference ≥20%

Continued

Study	*Compared indicator of infection*	*Adjustment*	*Percentage of positive cases (%) <u>or</u> means of antibody levels (m) in study populations (95% CI)*	*Statistical analysis*	*Summary* Infectious rate in South Asians vs. White Europeans
Boxall E, et al. (1994) [45]	**Hepatitis C Virus** (HCV): Proportion of seropositive cases	None	(%) W: 0.25 (0.01-0.49) † SA: 0.08 (-0.08-0.24) †	PRR=0.32 (0.05-2.10) †	**Lower** Statistically <u>not</u> significant Difference ≥20%
	Hepatitis B Virus (HBV): Proportion of seropositive cases	None	(%) W: 0.0 (-0.4-0.4) † SA: 1.04 (0.47-1.57) †	PRR=infinite †	**Higher** Statistically significant Difference ≥20%
Euler GL et al (2003) [46]	**Hepatitis B Virus** (HBV): Proportion of seropositive cases (95%CI)	Prenatal care, source of pay, age, year of infant's birth	(%) W: 0.6 (0.3-1.1) SA: 3.2 (0.8-8.7)	PRR=5.69 (2.58-12.55) †	**Higher** Statistically significant Difference ≥20%
Villari P, et al. (2001) [47]	**Hepatitis G Virus** (HGV): Proportion of seropositive cases	None	(%) W: 12.6 (9.2-16.1) † SA: 12.7 (5.3-20.0) †	PRR=1.01 (0.53-1.85) †	**No difference** Statistically not significant Difference <20%
Cortina-Borja M et al. (2004) [48]	**Human Immunodeficiency Virus** (HIV): Proportion of seropositive cases	None	(%) W: 0.04 (0.03-0.05) † SA: 0.02 (0.01-0.03) †	PRR=0.50 (0.25-0.96) †	**Lower** Statistically significant Difference ≥20%
Talukder YS, et al. (2007) [49]	**Varicella Zooster Virus** (VZV): Proportion of seropositive cases	None	(%) W: 93.6 (90.5-96.4) † SA: 85.7 (83.3-88.2) †	PRR=0.92 (0.89-0.96) †	**Lower** Statistically significant Difference <20%
O'Brien et al. (2009) [50]	**Cytomegalovirus** (CMV): Proportion of seropositive cases	Sex, day care attendance, breastfeeding duration, mother's age, occupation, marital status, education, number of people in the household	(%) W: 26.5 (22.1-30.7) † SA: 50.0 (31.8-68.2) †	PRR=1.96 (1.27-2.70) †	**Higher** Statistically significant Difference ≥20%

Continued

Study	*Compared indicator of infection*	*Adjustment*	*Percentage of positive cases (%) **or** means of antibody levels (m) in study populations (95% CI)*	*Statistical analysis*	***Summary*** Infectious rate in South Asians vs. White Europeans
C. Non-specific markers of infection					
Fischbacher CM et al. (2003) [51]	**Total IgG level:** Mean in blood samples (g/L)	Age, sex, smoking status	(m) W: 7.4 (6.7 - 8.2) SA: 13.5 (12.1-15.2)	OR=1.75 (1.48-2.08)	**Higher** Statistically significant Difference ≥20%
Miller MA et al. (2009) [52]	**Endotoxin level:** Geometric mean in blood samples (Eu/mL)	age, sex total cholesterol level	(m) W: 10.9 (9.8-12.1) SA: 13.3 (12.0-14.7)	p=0.013 p=0.001	**Higher** Statistically significant Difference ≥20%
		insulin level HDL level triglyceride level		p=0.371 p=0.321 p=0.411	**Higher** Statistically <u>not</u> significant Difference ≥20%

W, White European; SA, South Asian,
CI, Confidence Interval; OR, Odds Ratio; PRR, Prevalence Rate Ratio
cfu, Colony Forming Unit
† additional analysis by author

Appendix 1 (search strategies)

Search strategy for ***Medline*** (Compiled after consultation with librarian: Marshall Dozier, University of Edinburgh):

south asia*, asian india*, india*, pakistan*, bangladesh*, sri lanka*, exp Ethnic Groups/ **AND** exp "bacterial infections and mycoses"/, exp Parasitic Diseases/, exp Virus Diseases/, pathogen burden*, exp Cytomegalovirus Infections/, exp Chlamydia Infections/, cmv, exp Helicobacter Infections/, hsv, exp Herpes Simplex/, exp Mycobacterium tuberculosis/, exp Periodontitis/, exp Gingivitis/, exp Porphyromonas gingivalis/, exp Influenza, Human/, exp Immunoglobulin G/, exp Immunoglobulin M/, exp Immunoglobulin A/, **AND** exp North America/, exp Europe/, exp Australia/, **AND** exp Epidemiologic Methods/, exp comparative study/, **NOT** exp American Native Continental Ancestry Group/

Search strategy for ***Web of Science***

south asia* or asian india* or india* or pakistan* or bangladesh* or sri lanka* or ethnic* **AND** infection* **AND** epidemiologic study* or comparative study* or case control* or cohort* or cross sectional* or seroepidemiology* or seroprevalence*

Search strategy for ***GoogleScholar:***

- with all of the words: infection, ethnic groups
- with at least one of the words: south asia* or asian india* or india* or pakistan* or bangladesh* or sri lanka*
- without the words: "american indian"

<u>Appendix 2</u> (quorum diagram)

All results of electronic database search:
N=4883

→ Articles excluded by title, abstract and duplicate search:
N=4771

↓

Potential relevant articles:
N=112

→ Articles excluded due to the following reasons **(N= 91):**

- Reports ethnic variation among patients who were diagnosed with infectious disease (case series):
  N=31
- Examines "Asian" populations without evidence that they were of Indian subcontinent origins:
  N=22
- Describes South Asian population without White European comparison group:
  N=13
- Describes South Asians who live in South Asia:
  N=11
- Reports local infections with low potential to contributing a generalised atherosclerotic process:
  N=9
- Reports no indicator of infection:
  N=5

↓

Articles included in the review:
N=21

Appendix 3 (list of relevant but excluded papers)

Examines "Asian" populations without evidence that they were of Indian subcontinent origins:

- Badami KG, et al. Cytomegalovirus seroprevalence and 'cytomegalovirus-safe' seropositive blood donors. *Epidemiol Infect*. 2009;137:1776-80.
- Zajacova A, Dowd JB, Aiello AE.: Socioeconomic and race/ethnic patterns in persistent infection burden among U.S. adults. *J Geront A Biol Sci Med Sci*. 2009;64:272-9.
- Tindberg Y, et al. The accuracy of serologic diagnosis of Helicobacter pylori infection in school-aged children of mixed ethnicity. *Helicobacter*. 2001;6:24-30.
- Verdú EF, et al. Prevalence of Helicobacter pylori infection and chronic dyspeptic symptoms among immigrants from developing countries and people born in industrialized countries. *Digestion*. 1996;57:180-5.

Reports local infections with low potential to contributing a generalised atherosclerotic process:

- Tariq S, et al. Sexual health services for South Asians in London, UK: a case-control study. *Int J STD AIDS.* 2007;18:563-4.
- Versi E, et al. Bacteriuria in pregnancy: a comparison of Bangladeshi and Caucasian women. *Int Urogynecol J Pelvic Floor Dysfunct*. 1997;8:8-12.
- Skinner CJ, Saulsbury NK, Goh BT. Sexually transmitted infections in Bangladeshis resident in the UK: a case-control study. *Sex Transm Infect.* 2002;78:120-2.
- Simms I, et al. The English National Chlamydia Screening Programme: variations in positivity in 2007/2008. *Sex Transm Dis*. 2009;36:522-7.
- Fenton KA, et al. Ethnic variations in sexual behaviour in Great Britain and risk of sexually transmitted infections: a probability survey. *Lancet*. 2005;365:1246-55.