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Title	Cardiovascular risk in South Asians living in Canada: a systematic review
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Reviewer 1	Kevin Bainey
Institution	University of Alberta, Medicine
General comments	Rana at al. performed a systematic review and meta-analysis of Canadian studies addressing cardiovascular risk in South Asians living in Canada. The differences in ethnic profile and risk factors are a highly regarded topic particularly in the Canadian landscape which prides itself on diversity and multi-cultural ethnicity. Major comments: I would advise the authors review a similar systemic review published in Atherosclerosis (Atherosclerosis. 2009 May;204(1):1-10. doi: 10.1016/j.atherosclerosis.2008.09.023. Epub 2008 Oct 1. Review). This was a review focusing in the contributors of atherosclerosis in SA focusing on the predisposition towards the metabolic syndrome and diabetes. This review article should be mentioned particularly when highlighting the increased burden of CAD in SA. IN the methods section, I2 statistic was used to measure heterogeneity. What values were considered heterogeneous? I assume you used a 0-30, 30-60. 60-90, 90-100 cut-off. Please define. The NOS was used to evaluate non-randomized studies. I thought the scale was from 1-8 [selection (4 criterion), comparability (1 criterion) and outcome (3 criterion)]. Please clarify. To explore good quality studies, a NOS score of ≥5 was used. Why was this value chosen? Please clarify. In the discussion, the authors suggest a national surveillance system for non-communicable diseases. I agree with the concept but it must be done right. In the US, ethnic outcomes are followed. However, South Asians, East Asians, South-east Asians are all classified as 'Asian'. We need to ensure our classification system is done correctly. This may be worthy of mention in the discussion. The metabolic profile of the SA has been well characterized in this review. The 'visceral fat thin muscle' phenotype needs to be addressed. This leads to the increased risk of insulin resistance and diabetes which is so prevalent in this population. The role of adipokines should be mentioned in this section – Gupta et al in Circulation did a nice review of this concept. Perhaps mention of the 'thrifty gene' may be a possible explanation. This section needs to be expanded as this is one of the major drivers for premature CAD in the SA population. It is important to expand on the diabetic story. Looking at the forest plot, the test for heterogeneity was 0%. The point estimates all favor higher rates of diabetes in SA. This deserves an entire separate paragraph in the discussion with possible explanations – i.e. Neels thrifty gene hypothesis. There is also some genetic data suggesting predisposition towards diabetes in relation to genetic polymorphisms (PPAR-2, PC-1K). As for diagnostics and therapeutics of CVD, I'm not sure there are discriminatory factors for angiography. I agree with the Toronto data (as opposed to the Alberta data) especially since the SA population is greater in Ontario. While interesting, I think further evaluation is required to explore the potential of this paradox. As for outcomes, I'm not sure we have enough data to report 'long-term' outcome. It may be worthwhile mentioning the longest follow-up reported in the literature. I would like to see outcomes beyond 10-years with revascularization (particularly with CABG). To my knowledge, this has never been explored. Any information on medication complicance? This would be important for long-term outcomes regardless of treatment strategy (medical, PCI, CABG). Cardiac rehabilitation. Canadian data is interesting and nicely highlighted in the discussion. Was medication compliance captured? Are there any outcome data on SA versus WC whom completed CR? Should we consider ethnic based CR programs for particular groups? I would refer to the Calgary specialty CR program which caters to the SA population. I would consider a separate paragraph in the discussion regarding health status and quality of

	life in SA with CAD. Minor Comments: Reference 9 and 10 are written incorrectly.
Reviewer 2	Jeffrey Bakal
Institution	University of Alberta, Canadian VIGOUR Centre
General comments	Anand et al. present a meta analysis of CV risk in South Asians living in Canada. Overall they present a detailed summary of their analysis of pt features and comparisons. I am not convinced that all figures are necessary to demonstrate the results of interest.Also the figures should be cleaned up a but as the included text is difficult to read. In the primary analysis the use of units, confidence intervals and p values needs to be addressed more carefully to help with the understanding of the report. e.g., page 7 line 20 has no units line 23 has no p value with reference to the body fat percentage you should be clear that the differences are in absolute percentage etc. Additionally the reported results vary from confidence intervals to +/- SD/SE and back again. it would be helpful to consider a since format wherever possible. Also on page 10 line 11 there is a comparison made with no understanding of the variability, difference or significance in the result
Reviewer 3	Therese Tillin
Institution	Not specified.
General comments	A well written manuscript based on a thorough study regarding an important topic . Comments: There is a lack of description of what constitutes 'heart disease' or CVD. The methods on search strategy and selection are a little thin on detail. My main concerns relate to digestibility and the small number of high quality studies. My preference would be to see the supplementary tables 1 and 2 moved to the main text as these summarise the key findings, and that CVD and all other outcomes should also be summarised in these tables. The figures could then be moved to the supplementary files. Alternatively, it might be better, in the main manuscript, to focus on a smaller number of outcomes where there are good quality data to support the analyses and to move other outcomes to supplementary files. One of your consistent findings, although not surprising, was the doubling of prevalence of diabetes in South Asians, yet this is not mentioned in the closure of your discussion or in the conclusions. Your conclusions perhaps need some qualifying with regard to access to diagnostic testing, interventions and outcomes after MI- I would suggest that the data supporting these conclusions may be weak, especially given that you report higher standardised mortality rates for CHD in Canadian South Asians- this could merit dicussion. Minor comments: You report 'heart disease' (but not stroke) as an outcome in the main manuscript, but stroke appears under heart disease in the supplementary fuller description of outcomes. Supplementary Table 1 is entitled 'summary of quantitative results', although it includes prevalent diabetes and hypertension. Refs 54 and 58 appear to be incorrect (I haven't checked other references exhaustively) The paper by Kayaniyil (ref 66) does not appear in table 1. Grunau (ref 65) is misspelt in table 1.
Author response	**Reviewer 1:**

	Rana at al. performed a systematic review and meta-analysis of Canadian studies addressing cardiovascular risk in South Asians living in Canada. The differences in ethnic profile and risk factors are a highly regarded topic particularly in the Canadian landscape which prides itself on diversity and multi-cultural ethnicity. Major comments: 1. I would advise the authors review a similar systemic review published in Atherosclerosis (Atherosclerosis. 2009 May;204(1):1-10. doi: 10.1016/j.atherosclerosis.2008.09.023. Epub 2008 Oct 1. Review). This was a review focusing in the contributors of atherosclerosis in SA focusing on the predisposition towards the metabolic syndrome and diabetes. This review article should be mentioned particularly when highlighting the increased burden of CAD in SA. Thank you for pointing this out. In the revised version of the paper we have introduced the suggested reference. In particular, we have referenced the article when explaining CVD burden in SA in the introduction section: "The initial research suggests that one group in particular, those of SA origin (i.e. from India, Pakistan, Sri Lanka, Nepal, and Bangladesh) have higher CVD rates compared to the general population(10-13)". 2. In the methods section, I2 statistic was used to measure heterogeneity. What values were considered heterogeneous? I assume you used a 0-30, 30-60. 60-90, 90-100 cut-off. Please define. We apologize for not including the criteria in the paper. We used the cut-offs described by Higgins et al.(14) for interpreting the I2 statistics: • 0% to 25%: low heterogeniety; • 25% to 50%: moderate heterogeneity; • 50% to 75%: substantial heterogeneity; • 75% to 100%: considerable heterogeneity. 3. The NOS was used to evaluate non-randomized studies. I thought the scale was from 1-8 [selection (4 criterion), comparability (1 criterion) and outcome (3 criterion)]. Please clarify. Thank you for pointing this out. Indeed, we did not use the conventional NOS. We used a custom quality score (please see table below), modified from the NOS, that assessed 1) appropriateness of research design; 2) recruitment strategy; 3) response rate; 4) representativeness of sample; 5) objectivity/reliability of outcome determination; 6) power calculation provided; 7) appropriate statistical analyses . Research design Appropriate? Appropriate recruitment strategy? Response rate >75% of contacted? Is sample representative? Objective and reliable measures? Power calculation? Appropriate statistical analysis? 4. To explore good quality studies, a NOS score of ≥5 was used. Why was this value chosen? Please clarify. The median quality score was 4/7. However, we chose a cut-off of '5', because we felt that many of the studies that scored '4' would have been misclassified as high quality because they had serious limitations with respect to recruitment strategy i.e. a large proportion of studies rated '4' or less used convenience sampling. We recognize this is arbitrary, but we feel no more so than choosing a median value. 5. In the discussion, the authors suggest a national surveillance system for non-communicable diseases. I agree with the concept but it must be done right. In the US, ethnic outcomes are followed. However, South Asians, East Asians, South-east Asians are all classified as 'Asian'. We need to ensure our classification system is done correctly. This may be worthy of mention in the discussion. Thank you. As suggested, in the revised version of the paper a sentence was introduced to address the issue of classification of 'Asian' ethnicity. Specifically, the following sentence has been included in the discussion section: "However, some inter-study variation in these results exists which we attribute to differences in the classification of ethnicity (i.e. self report vs. direct assessment vs. surname classification), heterogeneity across "South Asian" populations

	(i.e. Pakistani vs. Indian vs. Bangladeshi, etc.) and classification of outcomes (self report vs. health administrative data)." 6. The metabolic profile of the SA has been well characterized in this review. The 'visceral fat thin muscle' phenotype needs to be addressed. This leads to the increased risk of insulin resistance and diabetes which is so prevalent in this population. The role of adipokines should be mentioned in this section – Gupta et al in Circulation did a nice review of this concept. Perhaps mention of the 'thrifty gene' may be a possible explanation. This section needs to be expanded as this is one of the major drivers for premature CAD in the SA population. We agree that adipokines play an important role in these conditions. We have now addressed the role of adipokines in the discussion section of our paper. Specifically, the following sentence was added to the paper: "This greater insulin resistance in South Asians may be due to altered levels and actions of adipokines(15)". We chose not to include a comment on the thrifty gene hypothesis as recent genetic studies of this concept have failed to find support for this concept(16). 7. It is important to expand on the diabetic story. Looking at the forest plot, the test for heterogeneity was 0%. The point estimates all favor higher rates of diabetes in SA. This deserves an entire separate paragraph in the discussion with possible explanations – i.e. Neels thrifty gene hypothesis. There is also some genetic data suggesting predisposition towards diabetes in relation to genetic polymorphisms (PPAR-2, PC-1K). While we agree with the reviewer that the ongoing studies addressing the genetic predisposition of SA to develop type 2 diabetes are important, we do no think this manuscript will allow us to do justice to a thorough review of the existing literature. We are aware of an ongoing meta-analysis of this particularly topic by Sohani et al. 8. As for diagnostics and therapeutics of CVD, I'm not sure there are discriminatory factors for angiography. I agree with the Toronto data (as opposed to the Alberta data) especially since the SA population is greater in Ontario. While interesting, I think further evaluation is required to explore the potential of this paradox. As for outcomes, I'm not sure we have enough data to report 'long-term' outcome. It may be worthwhile mentioning the longest follow-up reported in the literature. I would like to see outcomes beyond 10-years with revascularization (particularly with CABG). To my knowledge, this has never been explored. We agree data beyond 10 years will be informative. However, the available data is relatively short term and long-term data is not available for Canadian SA. 9. Any information on medication compliance? This would be important for long-term outcomes regardless of treatment strategy (medical, PCI, CABG). We agree that this is an important consideration; however, we did not design our search to look specifically for data regarding medication compliance, but a brief review of the literature among SA in Canada indicates it is sparse. 10. Cardiac rehabilitation. Canadian data is interesting and nicely highlighted in the discussion. Was medication compliance captured? Are there any outcome data on SA versus WC whom completed CR? Should we consider ethnic based CR programs for particular groups? I would refer to the Calgary specialty CR program which caters to the SA population. We agree that this is an important consideration; however, we could not identify any published papers which outlined the Calgary CR program. 11. I would consider a separate paragraph in the discussion regarding health status and quality of life in SA with CAD. Thank you for this suggestion. We found limited data reporting the health status and quality of life in SA with CVD. We discuss the literature on quality of life in SA with CVD in Supplementary Appendix 2. "One study reported the health status after MI in SA and WC patients. In a database review by Bainey 2011(17), SA in Alberta were more likely to report poor health status, as measured by Seattle Angina Questionnaire (SAQ), at 1 year after angiography. SAQ is a self-reported measure of health status where lower scores indicate poor health. The mean scores for angina frequency (86±23 vs. 88±20, p<0.001), treatment satisfaction (86±19 vs. 89±16, p<0.001) and quality of life (QOL) (71±24 vs. 76±21, p<0.001) were significantly lower in SA. There were no significant differences in angina stability (77±28

vs. 77±27, p=0.627) and exertional capacity (75±23 vs. 80±23, p=0.11)".
We have also included the following in discussion: "Moreover, SA with established CVD report worse health related quality of life outcomes (HRQOL) 1 year after angiography when compared to WC with CVD(17)".

Minor Comments:
12. Reference 9 and 10 are written incorrectly.

Thank you for pointing this out. The references have now been fixed.

Reviewer 2:

Anand et al. present a meta-analysis of CV risk in South Asians living in Canada. Overall they present a detailed summary of their analysis of pt features and comparisons.

1. I am not convinced that all figures are necessary to demonstrate the results of interest. Also the figures should be cleaned up a bit as the included text is difficult to read.

We apologize for the large number of figures. We have cleaned up the figures to make them legible and have reduced the number of figures from the paper. In particular, we have removed figures on obesity and waist circumference.

2. In the primary analysis the use of units, confidence intervals and p values needs to be addressed more carefully to help with the understanding of the report.
• e.g., page 7 line 20 has no units
• line 23 has no p value
• with reference to the body fat percentage you should be clear that the differences are in absolute percentage etc.

We apologize for the inconsistencies. In the revised version of the paper we have now clearly specified the units, CIs and p-values. Specifically, page 7 line 20 and 23 have been modified to, "The evidence suggests that SA in Canada have a higher age standardized incidence rate (/1000/year) of acute MI (SA Men: 4.97 vs. WC Men: 3.29, p<0.001; SA Women: 2.35 vs. WC Women: 1.53, p=0.01)(18) and prevalence of CVD (SA:5.7%-10.0% vs. WC:5.4-5.7%, p<0.05) as compared to non-SA(11,12,18)".

We have clarified that the differences are in absolute percentage with reference to body fat. We have revised the body fat section to: "At similar BMIs)(10,11,1-2,19), when compared to WC, SA have higher percent body fat [Men Absolute MD: 3.23% (95% CI: 0.83, 5.62; p=0.008), Women Absolute MD: 4.09% (95% CI: 3.46, 4.72; p<0.00001)])(19,20,21)".

3. Additionally the reported results vary from confidence intervals to +/- SD/SE and back again. it would be helpful to consider a since format wherever possible.

We agree, and apologize for the inconsistencies; however in some cases, the data were not sufficient for us to compute a consistent measure of uncertainty, owing to differences in the way standard errors were calculated, and varying degrees of completeness for n's in each arm.

4. Also on page 10 line 11 there is a comparison made with no understanding of the variability, difference or significance in the result

Thank you for catching this. In the revised paper, we have clarified the comparison made in line 11:
"Overall, SA appear to delay presentation to hospital with symptoms of acute myocardial infarction (AMI). In a study by Gupta 2002(22), the median time from symptom onset to presentation to the hospital was longer for SA than WC (3.92 v. 3.08 hrs, p =0.04)". No measures of variability were presented in the original paper.

Reviewer 3:

A well written manuscript based on a thorough study regarding an important topic.

Major comments:
1. There is a lack of description of what constitutes 'heart disease' or CVD.

Thank you. We have now added a description of CVD in the Prevalence and incidence of CVD

	Section: "defined as a history of myocardial infarction (MI), angina, silent MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG) or stroke". 2. The methods on search strategy and selection are a little thin on detail. We apologize for not including details on our search strategy. We have now added more details on the search strategy and selection in the revised paper. In particular, we have included the following paragraph: "Three investigators (AR, RdS, and SSA) screened titles and abstracts of the studies identified by the electronic search to arrive at a list of articles for full text review. The same reviewers assessed the eligibility of these full-text articles in triplicate. Disagreements were resolved by discussion and consensus. Studies that were not published as full reports, such as conference abstracts and letters to the editors were excluded". 3. My main concerns relate to digestibility and the small number of high quality studies. My preference would be to see the supplementary tables 1 and 2 moved to the main text as these summarise the key findings, and that CVD and all other outcomes should also be summarised in these tables. The figures could then be moved to the supplementary files. Alternatively, it might be better, in the main manuscript, to focus on a smaller number of outcomes where there are good quality data to support the analyses and to move other outcomes to supplementary files. We agree that the manuscript is dense. We have revised the paper to move the outcomes with limited data (food intake, physical activity, socioeconomic status and novel markers) to Supplementary Appendices, and have focused the main text on the better quality data. 4. One of your consistent findings, although not surprising, was the doubling of prevalence of diabetes in South Asians, yet this is not mentioned in the closure of your discussion or in the conclusions. Thank you for pointing this out. We agree that this finding is worthy of discussion. We have added the following to our conclusions: "Compared to WC, SA living in Canada have a higher prevalence and incidence of CVD, have twice the burden of diabetes and have a different cardiovascular risk profile". We also discuss higher insulin resistance in South Asians in detail. "The studies to date suggest that, even at conventionally "normal" BMI ranges, Canadian SA have higher body fat %, increased visceral abdominal fat and greater insulin resistance(11,23) compared with WC. These findings are consistent with previous studies in the U.K.(24) and the U.S.A.(24,25) of immigrant SA. This greater insulin resistance in South Asians may be due to altered levels and actions of adipokines(26). The reasons for South Asians' predisposition to this cardio-metabolic risk profile are still not well known, and may be due to complex biological interactions between genetic and environmental factors". 5. Your conclusions perhaps need some qualifying with regard to access to diagnostic testing, interventions and outcomes after MI- I would suggest that the data supporting these conclusions may be weak, especially given that you report higher standardised mortality rates for CHD in Canadian South Asians- this could merit discussion. We agree, we think that more research is required to better understand the trends in access to diagnostic testing, interventions and outcomes after MI. We mention the following in discussion: "We did not find any differences in short or long-term mortality after MI, however more data are required to understand the short-term clinical patterns after MI among SA in Canada, as this may reflect variations in health systems. Furthermore, studies in the U.K.(27-29) are conflicting: some studies show higher post-operative mortality while others show similar mortality rates between the two groups". Minor comments: 6. You report 'heart disease' (but not stroke) as an outcome in the main manuscript, but stroke appears under heart disease in the supplementary fuller description of outcomes. Thank you. We have added a definition of CVD in the main paper: "defined as a history of myocardial infarction (MI), angina, silent MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG) or stroke". 7. Supplementary Table 1 is entitled 'summary of quantitative results', although it includes prevalent diabetes and hypertension. We apologize for the lack of clarity. By "quantitative", we refer to those outcome measures

	that could be pooled in a meta-analysis, including prevalence odds ratios. In this table, we include all results that have been meta-analyzed (including prevalence of diabetes, hypertension and diabetes). Mean Difference (M.D.) were reported for continuous outcomes and prevalence odds ratio (O.R.) were reported for dichotomous outcomes. 8. Refs 54 and 58 appear to be incorrect (I haven't checked other references exhaustively) Thank you for pointing this out to us, we have corrected our reference list. 9. The paper by Kayaniyil (ref 66) does not appear in table 1. We did not include Kayaniyil et al. in table 1 as it was used in the discussion section and was not our primary outcome paper. 10. Grunau (ref 65) is misspelt in table 1. Thank you for catching this. Grunau et al. was not our primary outcome paper and has been removed from table 1. References 1. Foulds, H. J., Bredin, S. S., Warburton, D. E. Greater prevalence of select chronic conditions among Aboriginal and South Asian participants from an ethnically diverse convenience sample of British Columbians. Applied Physiology, Nutrition, and Metabolism. 2012;37(6), 1212-1221. 2. García-Bailo, B., Karmali, M., Badawi, A., El-Sohemy, A. (2013). Plasma 25-Hydroxyvitamin D, Hormonal Contraceptive Use, and Cardiometabolic Disease Risk in an Ethnically Diverse Population of Young Adults. Journal of the American College of Nutrition. 2013:32(5), 296-306. 3. García-Bailo B, Brenner D, Nielsen D, Lee HJ, Domanski D, Kuzyk M, Borchers CH, Badawi A,. Karmali M, El-Sohemy A. Dietary patterns and ethnicity are associated with distinct plasma proteomic groups. The American journal of clinical nutrition. 2012; 95,(2): 352-361. 4. Gasevic D, Khan N, Qian H, Karim S, Simkus G, Quan H, Mackay MH, Blair JO, Ayyobi AF. Outcomes following percutaneous coronary intervention and coronary artery bypass grafting surgery in Chinese, South Asian and white patients with acute myocardial infarction: administrative data analysis. BMC cardiovascular disorders. 2013;13, (1): 121. 5. Gupta M, Martineau P, Tran T, Despres JP, Gaw A, de Teresa E, et al. Low-density lipoprotein cholesterol and high-sensitivity C-reactive protein lowering with atorvastatin in patients of South Asian compared with European origin: insights from the Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study. Journal of clinical pharmacology. 2012;52(6):850-8. 6. Kohli, S., Lear, S. A. Differences in subcutaneous abdominal adiposity regions in four ethnic groups. Obesity. 2013;21(11):2288-2295. 7. Jones DA, Rathod KS, Sekhri N, Junghans C, Gallagher S, Rothman MT, et al. Case fatality rates for South Asian and Caucasian patients show no difference 2.5 years after percutaneous coronary intervention. Heart. 2012;98(5):414-9. 8. Shah BR, Victor JC, Chiu M, Tu JV, Anand SS, Austin PC, Manuel DG, Hux JE. Cardiovascular complications and mortality after diabetes diagnosis for South Asian and Chinese patients: a population-based cohort study. Diabetes Care. 2013 Sep;36(9):2670-6. 9. Trop S, Marshall JC, Mazer CD, Gupta M, Dumont DJ, Bourdeau A, et al. Perioperative cardiovascular system failure in South Asians undergoing cardiopulmonary bypass is associated with prolonged inflammation and increased Toll-like receptor signaling in inflammatory monocytes. The Journal of surgical research. 2014;187(1):43-52. 10. Chiu M, Austin PC, Manuel DG, Tu JV. Cardiovascular risk factor profiles of recent immigrants vs long-term residents of Ontario: a multi-ethnic study. The Canadian journal of cardiology. 2012;28(1):20-6. 11. Anand SS, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). The Lancet. 2000;356(9226):279-84. 12. Chiu M, Austin PC, Manuel DG, Tu JV. Comparison of cardiovascular risk profiles among ethnic groups using population health surveys between 1996 and 2007. CMAJ : Canadian Medical Association journal. 2010;182(8):E301-10. 13. Bainey KR, Jugdutt BI. Increased burden of coronary artery disease in South-Asians living in North America. Need for an aggressive management algorithm. Atherosclerosis.

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