

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Comorbidities, complications, and mortality in people of South Asian ethnicity with type 1 diabetes compared to other ethnic groups: a systematic review.
AUTHORS	Sarwar, Komil; Cliff, Phoebe; Saravanan, Ponnusamy; Khunti, Kamlesh; Nirantharakumar, Krishnarajah; Narendran, P

VERSION 1 - REVIEW

REVIEWER	Roger Parslow Senior Lecturer in Epidemiology School of Medicine University of Leeds UK
REVIEW RETURNED	23-Nov-2016

GENERAL COMMENTS	<p>This systematic review of risk factors and complications for type 1 diabetes in South Asian ancestry highlights the lack of organised data collection at a population level on this topic.</p> <p>The paper is long and a little repetitive in its presentation as under each outcome there is a list of findings. I suggest that you provide the comparative data under each outcome heading in a table with a summary of the findings. This would result in studies being cited more than once under the different outcome headings but would allow easy comparison of the findings under the outcomes. This would allow you to reduce your commentary that contains a lot of estimates and confidence intervals to a more manageable summary of the findings. Table 1 should be included as a supplementary file - it is important as this provides the extracted information for each study rather than outcome.</p> <p>I had very few other comments other than the following:</p> <p>Page 4, line 5: Grammar - Its.....</p> <p>Page 4, line 16: It's a matter of style but I think 'A study by...' is redundant - Just say 'Wille et al suggested.....'</p> <p>Page 4, lines 51/52 Your sentence suggests the risk factors are outcomes as their risk factor status only becomes evident at the end of the sentence. Smoking status is a different risk factor for complications to BMI, blood pressure etc. I think you should clarify that this is the only lifestyle factor you have included because of its importance. You should also note the relationship between smoking and other risk factors you have listed and it's direct effect on the outcomes.</p> <p>Page 15: have you considered the issue around competing risks? SAs with type 1 diabetes may die before developing retinopathy.</p>
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	Discussion: Have you considered the effect of increased adiposity in south Asians? Your BMI comparisons may need adjustment. See https://www.ncbi.nlm.nih.gov/pubmed/23592862
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REVIEWER	Ulrich Keller University of Basel, Div. Endocrinology and Diabetology, Switzerland
REVIEW RETURNED	29-Dec-2016

GENERAL COMMENTS	<p>The paper by Sarwar et al was reviewed. The title looks promising, but several issues need to be addressed:</p> <ol style="list-style-type: none"> 1. The studies included in the analysis are derived from a large range of years (1981 until 2015), a time period during which diabetes treatment and prevention of complications has changed dramatically. Therefore, the analysis should specifically consider studies which compared the different ethnic groups during the same period of observation with similar standards of therapy. 2. Blood pressure and lipid data should be supplemented if possible with data on the frequency of blood pressure and lipid medication (statin) use. It is unclear if differences in blood pressure and lipid parameters were due to differences in medication use between ethnic groups. 3. Data from patients with SA ethnicity living in the UK and in Asia or in South Africa were pooled. Are complication rates of SA immigrants and native SA patients the same? This should be discussed. 4. A problem of this study is the fact that some patients reported as "DM type 1" may have been in fact type 2, included as "IDDM"- particularly since some of the SA patients had features of DM type 2 (e.g. the mean BMI in the study by Sarwar et al 2015 was in the range of obesity) an HDL-C levels were lower than in WE patients. Unfortunately, waist circumference data or C-peptide levels were not reported. This point should be addressed.
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REVIEWER	Sunali Goonesekera Decision Resources Group, LLC, United States.
REVIEW RETURNED	23-Jan-2017

GENERAL COMMENTS	<ol style="list-style-type: none"> 1. Please include the search terms used to search relevant literature in the methods section. 2. Change the terms "risk factors" in the title and text to "comorbidities." Many of the "risk factors" listed such as SBP, BMI, and hypertension are not strong risk factors for type 1 DM (if they are, please cite references), and many of the papers included in this review have examined them as comorbidities of type 1 DM. Therefore, please replace the terms "risk factors" or "outcomes" used to describe these factors with the term "comorbidities." In addition, the value of HbA1C is a measure of disease control or severity rather than a risk factor for type 1 diabetes. 3. Briefly explain the rationale for evaluating smoking as a risk factor for type 1 DM, or leave it out. 4. Please clearly state criteria used to diagnose type 1 DM patients in the included studies in Table 1. 5. Replace the words "natural history" with "the progression of the disease," because natural history refers to the progression of the
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	<p>disease in the absence of treatment.</p> <p>6. Separate Table 1 into comorbidities (BMI, hypertension, etc.), and outcomes (nephropathy, retinopathy, mortality, etc.) and/or present results more clearly.</p> <p>7. Please briefly describe how South Asians compare to Caucasians with respect to comorbidities such as hypertension, hyperlipidemia, and obesity, in the general population, to provide readers with an idea of whether these differences are solely observed among type 1 DM patients.</p> <p>8. The conclusion that South Asian type 1 DM patients have higher mortality as compared to type 1 DM Caucasian patients was based on a single study. In addition, it is not clear whether this study adequately distinguished between type 1 DM patients and juvenile-onset type 2 DM patients. Therefore, this should be listed as a limitation.</p> <p>9. Please edit the manuscript further, especially in regard to punctuation. Make sure that numbers and abbreviations listed at the beginning of the sentences are spelled out.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Roger Parslow

Institution and Country: Senior Lecturer in Epidemiology, School of Medicine, University of Leeds, UK

Competing Interests: None declared.

This systematic review of risk factors and complications for type 1 diabetes in South Asian ancestry highlights the lack of organised data collection at a population level on this topic.

1) The paper is long and a little repetitive in its presentation as under each outcome there is a list of findings. I suggest that you provide the comparative data under each outcome heading in a table with a summary of the findings. This would result in studies being cited more than once under the different outcome headings but would allow easy comparison of the findings under the outcomes. This would allow you to reduce your commentary that contains a lot of estimates and confidence intervals to a more manageable summary of the findings. Table 1 should be included as a supplementary file - it is important as this provides the extracted information for each study rather than outcome.

Response: We have split the table into comorbidities and complications which makes it easier to read and interpret. We would prefer to keep Table 1 in the main text rather than as a supplementary file because it contains specific study details which we believe it is important for the readers to see. We hope this will be acceptable because there is only one other table in the article and this is a summary table.

I had very few other comments other than the following:

2) Page 4, line 5: Grammar - Its.....

Response: Corrected

3) Page 4, line 16: It's a matter of style but I think 'A study by...' is redundant - Just say 'Wille et al suggested.....'

Response: Corrected

4) Page 4, lines 51/52 Your sentence suggests the risk factors are outcomes as their risk factor status only becomes evident at the end of the sentence. Smoking status is a different risk factor for complications to BMI, blood pressure etc. I think you should clarify that this is the only lifestyle factor you have included because of its importance. You should also note the relationship between smoking and other risk factors you have listed and it's direct effect on the outcomes.

Response: This sentence has now been amended. We have removed smoking as a risk factor as

there was not enough information in the included studies regarding smoking as a lifestyle factor.

5) Page 15: have you considered the issue around competing risks? SAs with type 1 diabetes may die before developing retinopathy.

Response: We have included this issue around competing risk in our discussion

6) Discussion: Have you considered the effect of increased adiposity in south Asians? Your BMI comparisons may need adjustment. See <https://www.ncbi.nlm.nih.gov/pubmed/23592862>

Response: Previous literature has demonstrated how SA have increased adiposity in comparison to WE and have advocated lower cut-offs for BMI in SA; BMI > 23 overweight and BMI > 25 obese. We have included this in the discussion section.

Reviewer: 2

Reviewer Name: Ulrich Keller

Institution and Country: University of Basel, Div. Endocrinology and Diabetology, Switzerland

Competing Interests: None

The paper by Sarwar et al was reviewed. The title looks promising, but several issues need to be addressed:

1. The studies included in the analysis are derived from a large range of years (1981 until 2015), a time period during which diabetes treatment and prevention of complications has changed dramatically. Therefore, the analysis should specifically consider studies which compared the different ethnic groups during the same period of observation with similar standards of therapy.

Response: This point has been taken on board however there are extremely few papers that have been published that are relevant to our question. Therefore, to assimilate as much data as possible we have included all papers. We recognise the range of 25 years is a limitation of our study which we have included in the discussion section.

2. Blood pressure and lipid data should be supplemented if possible with data on the frequency of blood pressure and lipid medication (statin) use. It is unclear if differences in blood pressure and lipid parameters were due to differences in medication use between ethnic groups.

Response: Response: Unfortunately, the papers in our review did not include data on blood pressure and lipid medication use. This point has now been raised in our discussion section.

3. Data from patients with SA ethnicity living in the UK and in Asia or in South Africa were pooled. Are complication rates of SA immigrants and native SA patients the same? This should be discussed.

Response: Prevalence of T2DM is higher in migrant SA compared to native SA thought to be secondary to urbanisation and lifestyle. It is likely that prevalence and complication rates of T1DM would also be different in migrant and native SA and therefore grouping them together may cause inaccuracy of reporting of the results. This has now been included in our discussion section.

4. A problem of this study is the fact that some patients reported as "DM type 1" may have been in fact type 2, included as "IDDM"- particularly since some of the SA patients had features of DM type 2 (e.g. the mean BMI in the study by Sarwar et al 2015 was in the range of obesity) an HDL-C levels were lower than in WE patients. Unfortunately, waist circumference data or C-peptide levels were not reported. This point should be addressed.

Response: We accepted a clinical diagnosis for T1DM in the included studies. Some studies simply relied on coding of T1DM in their clinical systems as inclusion criteria with other studies accepting a younger age of diagnosis <30/35 years and insulin dependency as their inclusion criteria. As we did not have a standardised criterion for the diagnosis of T1DM for the included studies, it may well be that some patients with T2DM requiring insulin treatment may have been wrongly coded as having T1DM. This can lead to bias in the reporting of the results. This point has now been addressed in the discussion section.

Reviewer: 3

Reviewer Name: Sunali Goonesekera
 Institution and Country: Decision Resources Group, LLC, United States.
 Competing Interests: None declared

1. Please include the search terms used to search relevant literature in the methods section.

Response: The search terms have now been included in the methods section

2. Change the terms "risk factors" in the title and text to "comorbidities."

Many of the "risk factors" listed such as SBP, BMI, and hypertension are not strong risk factors for type 1 DM (if they are, please cite references), and many of the papers included in this review have examined them as comorbidities of type 1 DM. Therefore, please replace the terms "risk factors" or "outcomes" used to describe these factors with the term "comorbidities." In addition, the value of HbA1C is a measure of disease control or severity rather than a risk factor for type 1 diabetes.

Response: The term risk factors and outcomes have now been amended to comorbidities and complications where relevant

3. Briefly explain the rationale for evaluating smoking as a risk factor for type 1 DM, or leave it out.

Response: We have removed smoking as a risk factor for T1DM from our analysis

4. Please clearly state criteria used to diagnose type 1 DM patients in the included studies in Table 1.

Response: Unfortunately, some of the included papers did not state the criteria used to diagnose T1DM. They simply used coding of T1DM in their database as inclusion criteria. We have now amended Table 1 to include the criteria, where available, to diagnose T1DM.

5. Replace the words "natural history" with "the progression of the disease," because natural history refers to the progression of the disease in the absence of treatment.

Response: Changed to the above suggestion

6. Separate Table 1 into comorbidities (BMI, hypertension, etc.), and outcomes (nephropathy, retinopathy, mortality, etc.) and/or present results more clearly.

Response: Table 1 has been separated to comorbidities and complications as per the suggestion

7. Please briefly describe how South Asians compare to Caucasians with respect to comorbidities such as hypertension, hyperlipidemia, and obesity, in the general population, to provide readers with an idea of whether these differences are solely observed among type 1 DM patients.

Response: SA are at higher risk than White Europeans (WE) for the development of obesity and obesity-related diseases including insulin resistance, the metabolic syndrome, Type 2 Diabetes Mellitus (T2DM) and coronary heart disease. This has now been included in the background section.

8. The conclusion that South Asian type 1 DM patients have higher mortality as compared to type 1 DM Caucasian patients was based on a single study. In addition, it is not clear whether this study adequately distinguished between type 1 DM patients and juvenile-onset type 2 DM patients.

Therefore, this should be listed as a limitation.

Response: This has been listed as a limitation in the discussion section.

9. Please edit the manuscript further, especially in regard to punctuation. Make sure that numbers and abbreviations listed at the beginning of the sentences are spelled out.

Response: We have now addressed these edits.

VERSION 2 – REVIEW

REVIEWER	Ulrich Keller University of Basel Endocrine Practice, Basel
REVIEW RETURNED	07-Mar-2017

GENERAL COMMENTS	The paper has been improved after revision. The limitations are discussed.
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