PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and incidence of diabetes among Aboriginal people in remote communities of the Northern Territory, Australia: a retrospective, longitudinal data-linkage study
AUTHORS	Hare, Matthew; Zhao, Yuejen; Guthridge, Steven; Burgess, Paul; Barr, Elizabeth L. M.; Ellis, Elna; Butler, Deborah; Rosser, Amy; Falhammar, Henrik; Maple-Brown, Louise

VERSION 1 – REVIEW

REVIEWER	Falster, Kathleen University of New South Wales, Centre for Big Data Research in Health
REVIEW RETURNED	23-Dec-2021

GENERAL COMMENTS	This is a well written paper reporting the findings from a population-based retrospective cohort study (using data linkage) to describe the prevalence of diabetes in Aboriginal people living in remote areas in the Northern Territory of Australia. The introduction is nicely written overall. However, it would be useful if the authors could briefly acknowledge the different disease mechanisms for Type 1 versus Type 2 Diabetes and whether the concerns in the Aboriginal population in NT are primarily focused on the burden of Type 2 Diabetes. A few comments on the Results: Table 1: - It would be useful to see the median, IQR and range for HbA1C as well as the mean - Is there any reason not to include all individuals with prevalent diabetes during study period (counted once) in Table 1? A table disaggregated by year could be included in the appendix? Fig 2: It would also be useful to add lines for the prevalence of Type 2 and Type 1/other to visually illustrate that the high and increasing burden is primarily driven by T2D. Fig 3: The prevalence of diabetes is not visible for 0-9 years olds on this figure. Is there no data or just very low prevalence? A table insert at the bottom of the figure with exact numbers in males and females would be a nice addition to this figure to communicate the absolute scale of the problem. Fig 4: Are many of the <20y incident cases T1D or T2D? Given the different implications for prevention and treatment response, it would be useful to see this. For example, is there an earlier incidence of

	T2D in the Aboriginal population in the NT, if it isn't primarily T1D in younger age groups. The Discussion is nicely written overall. However, it would benefit from acknowledging that the high and increasing burden is predominantly Type 2 diabetes, as this has significant implications for prevention and treatment response. It would also be worth discussing why metformin was excluded from diabetes ascertainment, as explained in the appendix.

REVIEWER	Shepherd, Carrington Telethon Kids Institute
REVIEW RETURNED	27-Jan-2022

GENERAL COMMENTS	The manuscript reports on the prevalence and incidence of diabetes among Aboriginal people in remote NT over a seven-year period using linked clinical and administrative datasets. This is a very important topic given the substantial burden of cardiometabolic disease in the Aboriginal population and its role as a crucial driver of the health disparities with the non-Aboriginal population. The study gives real-world estimates of the burden and trends of diabetes that can inform public health policies. Overall, I thought the manuscript was an important contribution to the literature and is very well-written. I also appreciated the statement in the Methods pertaining to Patient and public involvement as it provided a clear understanding of the input of Aboriginal peoples and communities in the work – an issue too-often overlooked in quantitative empirical papers of this nature. Authors please note that Mr Marwan Ahmed (University of Western Australia) has assisted me in conducting this review. I have provided a few minor comments below, for consideration: Methods (page 6; lines 23-26): “The study included all Aboriginal clients, who were recorded as being local residents, of all remote health centres”. The author should provide a few more details about how remoteness was defined. Although the third paragraph of the Intro touched on remoteness (as did Figure 1), I still think a formal definition is important since the aim of the study is to assess diabetes in remote NT. Methods (page 6; lines 23-28): “The study included all Aboriginal clients, who were recorded as being local residents, of all remote health centres using the NT Health Primary Care Information System. This electronic medical record system is used in 51 out of 84 remote health services in the NT”. The Abstract gave the impression that this was a whole-population study, although I note that a number of centres in the in-scope geographic region are not included. The authors can perhaps provide more details about the differences between the included (n=51) and not included (n=33) health centres. Why do the 33 centres use systems other than NT Health Primary Care Information System? Are there any systematic (geographical, ethnic or heath service-related) differences between Aboriginal individuals recorded in the two types of centres, impacting the external validity? Methods (page 6; lines 30-32): “As the clinics are sole service providers in these communities, almost all the local population are clients”.

	Have the authors compared the number of records in a community with its total (census) population? Or has this been previously conducted in other studies? Methods (page 7; lines 5-10): “Individual level records were deterministically linked using a unique identifier, the Hospital Reference Number (HRN), which is used across all NT Health services. The HRN has been reliably used for deterministic linkage in previous studies.12”. I suggest the authors provide more details about how data linkage was performed. They can probably add the steps, validation processes, % of individuals linked across datasets and (if appropriate) diagrammatic explanation of the linkage. The provided reference (nr. 12) referred me to another reference (Li et al 2014 Dementia prevalence and incidence among the Indigenous and non-Indigenous populations of the Northern Territory), which in turn cites other studies when mentioning the reliability of HRN in linkage studies. Methods (page 7; line 28): Outcome definition The methods used to ascertain diabetes appear to be robust. Were these methods previously established, or are they the authors’ own? Methods (page 7; lines 33-36): “(ii) prescription of a diabetes medication according to Anatomical Therapeutic Chemical (ATC) classification code A10 other than Metformin” The authors can probably guide the reader to the validation supplement where the intuitive question ‘why: other that metformin?’ can be answered. Methods (page 7; lines 42-46): “Biochemical criteria included haemoglobin A1c (HbA1c) ≥6.5% (≥48 mmol/mol), fasting plasma glucose ≥7.0 mmol/L, 2-hour plasma glucose ≥11.1 mmol/L, and/or random capillary or plasma glucose ≥11.1 mmol/L.” References for guidelines from which these cut-offs are adapted can be added. Methods (page 8; line 10): statistical analysis What methods were used to calculate the confidence intervals? Results (Table 1) The table shows that, in the year 2018/2019, 47% of the Aboriginal people were not on glucose lowering therapy. This appears to be a high percentage. Is the percentage informative on the quality of diabetes management? If appropriate, the authors may consider discussing its possible implications (diabetes complications, relation with glycated haemoglobin), probably along with HbA1c. Discussion (page 10; 2nd paragraph) The authors compared the trends in diabetes prevalence with previous studies in the NT and United States (although only for illustrative purposes). Are there studies from other Australian states/territories? Discussion (page 11; 3rd paragraph) Given the higher rates and increasing concerns about gestational diabetes among Aboriginal women in recent years, can post-partum screening be a contributor to the high burden of diabetes reported in Aboriginal women relative to men?

	Discussion (page 12; 2nd and 3rd paragraphs) Diabetes incidence, despite being a main part of the study objective, is only discussed in relation to previous evidence. Perhaps the discussion of prevalence has already covered-off on all relevant issues about the burden of diabetes – if so, what did measuring the incidence add to the study? Discussion (page 14; 1st paragraph): Isn't there a possibility that Aboriginal people in CA are more likely to be screened for diabetes (given their previously reported higher prevalence). Are there differences in health services between TE and CE? Discussion (page 14; 2nd paragraph): "Our findings are unlikely to be generalisable to Aboriginal peoples living in urban centres or in other regions of Australia". Can the authors, please, briefly explain this statement?

REVIEWER	Jaruratanasirikul, Somchit Prince Songkla Univ, Pediatrics
REVIEW RETURNED	04-Feb-2022

GENERAL COMMENTS	This study is a retrospective cohort analysis describing the prevalence and burden of DM in among aboriginal people in remote communities of the Northern Territory, Australia (N=21 267). The diagnosis of DM was based on the data from hospital and primary care ICD-10 coding, prescription and biochemistry tests (HbA1c, plasma glucose) in 7 years (from 1 July 2012 to 30 June 2019). The diabetes incidence was assessed in aggregate over a three-year period (2016/17 to 2018/19). The prevalence of DM increased from 14.4% in 2012 to 17.0% in 2018 which was very high and increased with age (peak at 50s), mostly with type 2 (about 98%). The incidence rate in the total population in 2018/2019 was 7.9 per 1000 person-years with the peak incidence among 50-59 year-olds. The authors hypothesized for this high prevalence rate of DM was from multiple factors such as the transitions in daily lifestyle among the aboriginal people, the epigenetic factors during pregnancy (intrauterine exposure to hyperglycaemia or maternal undernutrition). The future burden of this high prevalence of diabetes was also mentioned. The strengths and limitations of the study are well stated. The legends for figures and Tables are well described.

REVIEWER	Mwita, Julius University of Botswana, Internal medicine
REVIEW RETURNED	13-Feb-2022

GENERAL COMMENTS	Well written manuscript. The study well described the increasing trend of the burden(prevalence) of diabetes in the studied population. For the reason stated (small numbers), the calculation of incidence rate was limited to one period: 2016/17 - 2018/19. Given what is already described by the trend of prevalence of diabetes, I don't think the calculated incidence rate add anything more. I would therefore describe the prevalence, and omit incidence, Results: When median is used in a sentence, it would be reasonable to state that whatever is in the bracket is IQR for a reader to

	understand. `~~~For instance; "Median age at baseline was 22 (9-39) years, ..." Results: For consistency, describe all the proportions with their 95% CI as seen in some sentences.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Kathleen Falster, University of New South Wales Comments to the Author:

This is a well written paper reporting the findings from a population-based retrospective cohort study (using data linkage) to describe the prevalence of diabetes in Aboriginal people living in remote areas in the Northern Territory of Australia.

The introduction is nicely written overall. However, it would be useful if the authors could briefly acknowledge the different disease mechanisms for Type 1 versus Type 2 Diabetes and whether the concerns in the Aboriginal population in NT are primarily focused on the burden of Type 2 Diabetes.

Response

We thank the reviewer for the positive feedback and have noted the different types of diabetes and their relevance in the introduction as recommended. The second paragraph has been amended as follows:

"Unlike type 1 diabetes, which is caused by insulin deficiency due to autoimmune-mediated pancreatic beta-cell failure, type 2 diabetes is characterised by insulin resistance and a degree of beta-cell dysfunction.[4] Indigenous populations are disproportionately affected by type 2 diabetes and associated complications.[5]"

Ref

4. Hare MJL, Topliss DJ. Classification and Laboratory Diagnosis of Diabetes Mellitus. In: Bandeira F, Gharib H, Griz L, Faria M, eds. Endocrinology and Diabetes. Springer, Cham: 2022:303-13.
5. Harris SB, Tompkins JW, TeHiwi B. Call to action: A new path for improving diabetes care for Indigenous peoples, a global review. Diabetes Res Clin Pract 2017;123:120-33.

A few comments on the Results:

Table 1:

- It would be useful to see the median, IQR and range for HbA1C as well as the mean

Response

The median (IQR) for HbA1c has been added to table 1. In doing so, we also noted that SI units for HbA1c (mmol/mol) had not been provided for the mean HbA1c, these have been added in addition to the commonly used NGSP % value (please note that the NGSP acronym is now the formal name for what used to be known as the National Glycohemoglobin Standardization Program).

- Is there any reason not to include all individuals with prevalent diabetes during study period (counted once) in Table 1? A table disaggregated by year could be included in the appendix?

Response

Thank you for the question. The rationale for presenting the data for the most recent year (2018/19) of the study period was to provide an up-to-date description of the population with prevalent diabetes. This is of public health relevance with regard to understanding the current burden and also has implications for service planning. Aside from people who have died or moved away from the included population centres, the 2018/19 data includes those with prevalent diabetes in earlier years. The table includes treatment and HbA1c data. We felt that providing data from the most recent year was the most valuable to inform clinicians, public health and policy makers. Including all individuals with prevalent diabetes during the study period (counted once) would just add a small number of people (those who've died or moved away), for whom the available treatment and HbA1c data will not be current. Therefore, our preference is to leave these results unchanged.

Fig 2: It would also be useful to add lines for the prevalence of Type 2 and Type 1/other to visually illustrate that the high and increasing burden is primarily driven by T2D.

Response

Thank you for this suggestion and we acknowledge that the presentation of our results has not sufficiently highlighted that we are primarily talking about type 2 diabetes throughout the manuscript. By 2018/19, the population prevalence of type 1 diabetes was only 0.17% (n/N=34/20,429) and the prevalence of other diabetes types was only 0.07% (n/N=14/20,429). Therefore, we have decided not to add these as separate lines on Figure 2. Due to the y-axis scale required to accommodate the prevalence of type 2 diabetes, the type 1 and other diabetes lines are essentially just overlapping flat lines along the x-axis. We have instead adjusted the footnote under the figure to note that what is reported is predominantly type 2 diabetes:

"Figure 2. Trend in crude diabetes prevalence among Aboriginal people (all ages) in remote NT communities over seven years. Error bars are 95% confidence intervals. Note the vast majority of

prevalent diagnoses were classified as type 2 diabetes (98.6% type 2, 0.17% type 1 and 0.07% other diabetes in 2018/19)."

We have also added an additional phrase to the first paragraph of the main text results as follows:

"By 2018/19 this prevalence had increased to 17.0% (95% CI: 16.5%-17.5%, n/N=3477/20 429), with 98.6% (n/N=3429/3477) of diagnoses classified as type 2 diabetes."

Fig 3: The prevalence of diabetes is not visible for 0-9 years olds on this figure. Is there no data or just very low prevalence? A table insert at the bottom of the figure with exact numbers in males and females would be a nice addition to this figure to communicate the absolute scale of the problem.

Response

We agree the very low prevalence rate in the 0-9 years age group cannot be seen due to the necessary scale of the y-axis to accommodate the high prevalence at older ages. Thank you for the suggestion. A table has been added below the graph. There is also a similar issue in figure 4 and so we have added data labels to show the incidence rates numerically.

Fig 4: Are many of the <20y incident cases T1D or T2D? Given the different implications for prevention and treatment response, it would be useful to see this. For example, is there an earlier incidence of T2D in the Aboriginal population in the NT, if it isn't primarily T1D in younger age groups.

Response

All but two of the 483 incident diabetes cases across all age groups were type 2 diabetes (99.6%). This finding is presented in the results section of the text. To better highlight this important consideration, we have added the following sentence to the footnote under the figure: "Out of 483 incident diabetes diagnoses, 481 (99.6%) were recorded as type 2 diabetes."

The Discussion is nicely written overall. However, it would benefit from acknowledging that the high and increasing burden is predominantly Type 2 diabetes, as this has significant implications for prevention and treatment response.

Response

Thank you for the recommendation. Communication of the fact that the burden relates almost entirely to type 2 diabetes has been strengthened. The contents of the discussion with regard to existing evidence, potential mechanisms and implications of the findings are already focussed on type 2 diabetes, it was just not sufficiently clearly stated.

The first two sentences of the discussion have been amended as follows:

“The burden of type 2 diabetes among Aboriginal people in remote communities of the NT, Australia, is immense and growing. Despite the relatively young age of this population, which includes children, we report a current diabetes prevalence of 17%, of which 99% is classified as type 2 diabetes.”

The first sentence of the second paragraph of the discussion has been amended as follows:

“The epidemic of type 2 diabetes among Aboriginal people in the remote NT has occurred in recent history and has continued to grow in the last few decades.”

The first sentence of the conclusion has been amended as follows:

“The burden of type 2 diabetes among Aboriginal people in remote communities of the NT is among the highest reported of any population globally despite the population being relatively young.”

It would also be worth discussing why metformin was excluded from diabetes ascertainment, as explained in the appendix.

Response

We agree it is important to mention this in the main text rather than just the appendix. We felt that it is neither a strength nor limitation, but rather one aspect of the methodology relating to outcome ascertainment. We have therefore added the following sentence to the Methods section:

“Metformin was excluded from the diabetes definition as it is commonly used for other indications, including polycystic ovarian syndrome and “pre-diabetes”.”

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Reviewer: 2

Dr. Carrington Shepherd, Telethon Kids Institute Comments to the Author:

The manuscript reports on the prevalence and incidence of diabetes among Aboriginal people in remote NT over a seven-year period using linked clinical and administrative datasets. This is a very important topic given the substantial burden of cardiometabolic disease in the Aboriginal population and its role as a crucial driver of the health disparities with the non-Aboriginal population. The study gives real-world estimates of the burden and trends of diabetes that can inform public health policies. Overall, I thought the manuscript was an important contribution to the literature and is very well-written. I also appreciated the statement in the Methods pertaining to Patient and public involvement

as it provided a clear understanding of the input of Aboriginal peoples and communities in the work – an issue too-often overlooked in quantitative empirical papers of this nature.

Authors please note that Mr Marwan Ahmed (University of Western Australia) has assisted me in conducting this review.

Response

Thank you for the positive feedback and appreciation of this public health priority area. It is also appreciated that the reviewer has acknowledged the critical importance of involving Aboriginal people and communities in this work.

I have provided a few minor comments below, for consideration:

Methods (page 6; lines 23-26): “The study included all Aboriginal clients, who were recorded as being local residents, of all remote health centres”.

The author should provide a few more details about how remoteness was defined. Although the third paragraph of the Intro touched on remoteness (as did Figure 1), I still think a formal definition is important since the aim of the study is to assess diabetes in remote NT.

Response

Thank you for this recommendation. The following sentence has been added to the Methods section:

“Each of these health services are in locations defined as either remote or very remote according to the Australian Statistical Geography Standard.[12] These remoteness classifications are based on relative accessibility to services in urban centres according to road distance measurements.”

Ref

12. Australian Bureau of Statistics. 1270.0.55.005 Australian Statistical Geography Standard (ASGS): Volume 5 - Remoteness Structure, July 2016. Canberra: Commonwealth of Australia; 2018.

Methods (page 6; lines 23-28): “The study included all Aboriginal clients, who were recorded as being local residents, of all remote health centres using the NT Health Primary Care Information

System. This electronic medical record system is used in 51 out of 84 remote health services in the NT”.

The Abstract gave the impression that this was a whole-population study, although I note that a number of centres in the in-scope geographic region are not included. The authors can perhaps provide more details about the differences between the included (n=51) and not included (n=33) health centres. Why do the 33 centres use systems other than NT Health Primary Care Information System? Are there any systematic (geographical, ethnic or heath service-related) differences between Aboriginal individuals recorded in the two types of centres, impacting the external validity?

Response

The reviewer raises an interesting issue that has been considered previously by the authorship group, which includes people who have worked in primary care services in the NT as clinicians, leaders and researchers for decades. We note that the abstract does not state that this is a whole-population study of the remote NT. However, we have adjusted the wording to improve clarity:

"Setting: Remote health centres using the NT Government Primary Care Information System (51 out of a total of 84 remote health centres in the NT).

Previously, all health services in the remote NT were administered by the Government. Over time, there has been a gradual transition to Aboriginal Community Controlled Health Organisations (ACCHOs) running some remote services. The ACCHOs are still government-funded and similarly provide universal free health care. The vast majority of health services included in this study are Government-administered but a small number have transitioned to ACCHO administration yet continue to use PCIS. For these services, appropriate additional governance requests to access data were made. Due to privacy concerns, we are not able to identify individual communities and can only report data in aggregate. The 33 remote health centres that are not included in our study are all administered by ACCHOs and do not use the same electronic medical record system.

It is not known whether there are any systematic differences between communities in the NT which have Government- versus ACCHO- administered health services. Given the lack of existing evidence and the inability to look at this in our study, the authors believe it would be inappropriate to speculate on this issue in the manuscript. However, it is known that there is great heterogeneity between Aboriginal people groups across the NT. This diversity is highlighted in the introduction and discussion of the manuscript. The 51 communities contributing data to this study are geographically spread across the NT (see Figure 1), however there is the potential for some bias to be introduced based on which communities have contributed data, which could impact the generalisability of the findings.

Discussion of this issue has been added to the limitations section of the discussion:

"Significant heterogeneity exists between Aboriginal communities across the NT. The inclusion of data in our study from most, but not all, remote communities in the region could have introduced some bias and limit the generalisability."

Methods (page 6; lines 30-32): “As the clinics are sole service providers in these communities, almost all the local population are clients”.

Have the authors compared the number of records in a community with its total (census) population? Or has this been previously conducted in other studies?

Response

There are substantial challenges in comparing census population estimates from the Australian Bureau of Statistics (ABS) with the populations serviced by clinics in remote NT communities due to the high mobility of Aboriginal people in this region. Service catchment areas also don’t closely match ABS statistical geography regions. In the Primary Care Information System (PCIS), clients are flagged as residents or visitors. A “usual clinic” is recorded for each individual client and these lists are routinely updated according to who is currently living in the community. The local clinic is responsible for their resident clients and will encourage local residents to complete routine specified services, including annual adult health checks. Including only resident clients in our study, minimises the risk of counting individuals in the numerator and/or denominator who have actually moved to another location and are thus “immortal” with regards to developing diabetes. It also prevents capture of data from individuals who may have sought care at one of the communities included in the study, but who usually reside elsewhere (such individuals, who are seeking healthcare acutely, are arguably more likely to have chronic conditions such as diabetes). Thus, while the sampling methodology is not perfect, we believe that use of the resident client population in PCIS provides reliable numerators and denominators for our diabetes estimates and that comparison to census data would not be a reliable means to validate the total population size in this particular instance.

Methods (page 7; lines 5-10): “Individual level records were deterministically linked using a unique identifier, the Hospital Reference Number (HRN), which is used across all NT Health services. The HRN has been reliably used for deterministic linkage in previous studies.12”.

I suggest the authors provide more details about how data linkage was performed. They can probably add the steps, validation processes, % of individuals linked across datasets and (if appropriate) diagrammatic explanation of the linkage.

The provided reference (nr. 12) referred me to another reference (Li et al 2014 Dementia prevalence and incidence among the Indigenous and non-Indigenous populations of the Northern Territory), which in turn cites other studies when mentioning the reliability of HRN in linkage studies.

Response

Thank you for highlighting the need for more detail here. The HRN and other identifiers are stored centrally in the NT Health Client Master Index which connects to the other NT Health information

systems. The accuracy of these records is subject to continual audit and review processes. The HRN is known to be a reliable linkage tool and has been used in multiple previous studies. The official data linkage agency for South Australia and Northern Territory, SA NT DataLink, employs the NT Health HRN as a key identifier for NT datasets and it has satisfied their reliability criteria for use in deterministic linkage (nb. SA NT DataLink was not employed for our study). A 2011 validation study (ref 11 previously, now ref 13 in the revised manuscript) compared demographic details in NT Health records with findings of detailed interviews with Aboriginal patients in hospital. The HRN from patients' hospital wrist bands was the sole identifier used to match questionnaire data with hospital admission records. A high level of accuracy was found for each data item, including sex (99%), Indigenous status (98%), district of residence (91%) and year of birth (91%). The following sentences have been added to the Methods:

"The HRN and other personal identifiers are routinely stored in a centralised Client Master Index, which connects to and synchronises across various NT Health information systems, including both PCIS and the Hospital Inpatient Activity dataset. The Client Master Index is subject to continual audit and review and is deemed reliable for deterministic linkage in research.[13,14]"

Refs

13. Foley M, Zhao Y, Condon J. Demographic data quality assessment for Northern Territory public hospitals 2011. Darwin: Northern Territory Government Department of Health; 2012.
14. Li L, Guthridge S, Li SQ, et al. Estimating the total prevalence and incidence of end-stage kidney disease among Aboriginal and non-Aboriginal populations in the Northern Territory of Australia, using multiple data sources. BMC Nephrol 2018;19:15.

Methods (page 7; line 28): Outcome definition The methods used to ascertain diabetes appear to be robust. Were these methods previously established, or are they the authors' own?

Response

The methods used were the authors' own based on standard approaches to the available coding, biochemistry and medication data. Biochemical criteria for the diagnosis of diabetes were as per standard Australian and international guidelines. Medications for diabetes were as per the WHO Anatomical Therapeutic Chemical (ATC) drug classification system, with the exception of metformin, which was excluded on the basis of our own validation analysis presented in the Appendix. Diabetes diagnostic codes were as per the ICD-10-AM and ICPC classifications, with some clarifications relating to defining diabetes type based on our own validation analyses for codes where the ICPC system is unclear. Our approach is presented in the methods section with additional details in the appendix.

Methods (page 7; lines 33-36): "(ii) prescription of a diabetes medication according to Anatomical Therapeutic Chemical (ATC) classification code A10 other than Metformin"

The authors can probably guide the reader to the validation supplement where the intuitive question ‘why: other that metformin?’ can be answered.

Response

Thank you for this suggestion. It was also raised by reviewer #1 and the following sentence has been added to the methods:

“Metformin was excluded from the diabetes definition as it is commonly used for other indications, including polycystic ovarian syndrome and “pre-diabetes”.”

The sentence following this one refers the reader to the validation supplement with regard to multiple aspects of the case ascertainment criteria.

Methods (page 7; lines 42-46): “Biochemical criteria included haemoglobin A1c (HbA1c) ≥6.5% (≥48 mmol/mol), fasting plasma glucose ≥7.0 mmol/L, 2-hour plasma glucose ≥11.1 mmol/L, and/or random capillary or plasma glucose ≥11.1 mmol/L.”

References for guidelines from which these cut-offs are adapted can be added.

Response

A reference to the Royal Australian College of General Practitioners guidelines for type 2 diabetes has been added. The RACGP diagnostic guidelines are consistent with WHO and ADA criteria for the diagnosis of type 2 diabetes.

Ref

15. The Royal Australian College of General Practitioners. Management of type 2 diabetes: A handbook for general practice. East Melbourne, Vic: RACGP; 2020.

Methods (page 8; line 10): statistical analysis What methods were used to calculate the confidence intervals?

Response

The methods section has been updated as follows:

“Annual diabetes prevalence (%) was calculated for the total population for each financial year (1st July to 30th June) between 2012/13 and 2018/19, with 95% confidence intervals calculated using: ˜±

1.96 ( )."

Results (Table 1)

The table shows that, in the year 2018/2019, 47% of the Aboriginal people were not on glucose lowering therapy. This appears to be a high percentage.

Is the percentage informative on the quality of diabetes management? If appropriate, the authors may consider discussing its possible implications (diabetes complications, relation with glycated haemoglobin), probably along with HbA1c.

Response

Thank you for noting this. We agree it is an important finding to highlight. A sentence relating to this has been added to the first paragraph of the discussion:

"This combination of young age of onset and severe chronic hyperglycaemia is likely to be accompanied by a high burden of diabetes complications and premature mortality.[18,19] Of additional concern is the high proportion of people meeting criteria for diabetes who were not prescribed glucose-lowering therapy (47%) despite the mean HbA1c being 7.9% (63 mmol/mol). This suggest a significant gap between established treatment recommendations and real-world implementation into practice."

Discussion (page 10; 2nd paragraph)

The authors compared the trends in diabetes prevalence with previous studies in the NT and United States (although only for illustrative purposes). Are there studies from other Australian states/territories?

Response

The main intent of this paragraph was to highlight the prevalence in the NT compared to historical data and to illustrate that the prevalence in Central Australian Aboriginal communities is as high as or higher than populations previously described as having the highest rates of diabetes globally. We acknowledge that there was little discussion of any existing evidence relating to temporal trends in diabetes prevalence. There are very few studies that have looked at temporal changes in diabetes epidemiology among Aboriginal people in any state/territory of Australia. The most recent data are in specific population groups, including pregnant women and children. Following on from the second paragraph of the discussion, an additional paragraph has been added as follows:

"There are limited published data examining temporal trends in diabetes epidemiology among Aboriginal people in Australia. An early study conducted in a single community in Central Australia, showed that the prevalence of diabetes increased from 11.6% in 1987 to 20.7% in 1995.[22] More recent studies from Western Australia and the NT have examined diabetes prevalence trends during pregnancy, showing substantial growth in the number of Aboriginal women with type 2 diabetes diagnosed prior to pregnancy.[23,24] In addition, the incidence of diabetes among Aboriginal and Torres Strait Islander children (aged under 16 years) in Western Australia increased considerably between 2000 and 2019.[25] Our findings add to this existing literature, showing an 18% increase in diabetes prevalence over seven years. Numerous factors, not assesed in our study, may have contributed to the observed change, such as increasing incidence, improved survival and greater uptake of screening."

Refs:

22. McDermott R, Rowley KG, Lee AJ, et al. Increase in prevalence of obesity and diabetes and decrease in plasma cholesterol in a central Australian Aboriginal community. Med J Aust 2000;172:480-4.
23. Ahmed MA, Bailey HD, Pereira G, et al. Trends and burden of diabetes in pregnancy among Aboriginal and non-Aboriginal mothers in Western Australia, 1998-2015. BMC Public Health 2022;22:263.
24. Hare MJL, Barzi F, Boyle JA, et al. Diabetes during pregnancy and birthweight trends among Aboriginal and non-Aboriginal people in the Northern Territory of Australia over 30 years. Lancet Reg Health West Pac 2020;1:100005.
25. Haynes A, Curran JA, Davis EA. Two decades of increasing incidence of childhood-onset type 2 diabetes in Western Australia (2000-2019). Med J Aus 2021;214:285-6.

Discussion (page 11; 3rd paragraph)

Given the higher rates and increasing concerns about gestational diabetes among Aboriginal women in recent years, can post-partum screening be a contributor to the high burden of diabetes reported in Aboriginal women relative to men?

Response

Thank you for the suggestion. This is a possible contributing factor. The fact that prevalence rates were markedly higher among girls than boys at young age and that this discrepancy persists into older age, suggests it would only have a minor contribution. It is more likely that the increasing rates of GDM reflect the growing prevalence of pre-existing impaired glucose regulation in young women, driven by the same aetiological factors as the growing rates of type 2 diabetes we have observed here. Our discussion notes the possibility that women participate in screening for diabetes more than men. Nevertheless, we have added the following sentence to the relevant paragraph in the discussion:

"Routine screening for diabetes during pregnancy and following a pregnancy complicated by gestational diabetes may also have an impact."

Discussion (page 12; 2nd and 3rd paragraphs) Diabetes incidence, despite being a main part of the study objective, is only discussed in relation to previous evidence. Perhaps the discussion of prevalence has already covered-off on all relevant issues about the burden of diabetes – if so, what did measuring the incidence add to the study?

Response

Much of our discussion around the potential mechanisms for the high burden of diabetes, the disparities between men and women and the implications of our findings apply to both prevalence and incidence. Many epidemiological studies are unable to report on incidence, which limits our ability over time to assess the contributions of positive factors, such as increased survival, to the growing prevalence of diabetes. Incidence is a much more useful measure for assessing the impact of public health strategies designed to prevent diabetes. We were unable to assess trends in incidence over time. So the key finding was the contemporary incidence rate, which we have endeavoured to compare to the existing limited evidence. We hope that future work can re-assess diabetes incidence in this population. The following sentence has been added to the discussion relating to incidence:

"Establishing the contemporary diabetes incidence rate in our study context is important for the future evaluation of public health strategies aimed at preventing diabetes."

Discussion (page 14; 1st paragraph):

Isn't there a possibility that Aboriginal people in CA are more likely to be screened for diabetes (given their previously reported higher prevalence). Are there differences in health services between TE and CE?

Response

While this is possible, we think it is unlikely to be a factor. The other findings comparing Central Australia and the Top End suggest less engagement in health care (higher HbA1c levels and fewer people with diabetes who had an HbA1c check in the last 12 months of the study period). It is also known that rates of preventable hospitalisations relating to diabetes and rates of kidney disease are significantly higher in Central Australia (1,2).

Refs:

1. Zhang X, Zhao Y. Potentially preventable hospitalisation in the Northern Territory 2005-06 to 2017-18. Accessed via: https://digitallibrary.health.nt.gov.au/prodjspui/bitstream/10137/11656/3/Potentially%20preventable%20hospitalisations%20in%20the%20Northern%20Territory%202005-06%20to%202017-18.pdf

2. Zhao Y, Connors C, Wright J, Guthridge S, Bailie R. Estimating chronic disease prevalence among the remote Aboriginal population of the Northern Territory using multiple data sources. Aust N Z J Public Health 2008;32:307-313.

A similar mix of health services exist in the Top End and Central Australia regions, but there are significant geographic and demographic differences. As discussed, there is also great diversity between Aboriginal people groups throughout the NT.

Discussion (page 14; 2nd paragraph): “Our findings are unlikely to be generalisable to Aboriginal peoples living in urban centres or in other regions of Australia”. Can the authors, please, briefly explain this statement?

Response

Thank you for bringing to our attention the broad nature of this statement. The findings may actually be relevant to remote communities in other jurisdictions. We have re-worded the sentence to focus more on the potential differences between urban and remote communities. The sentence has also been moved earlier in the paragraph so that it now follows on from a sentence (added in response to a comment above) relating to heterogeneity between Aboriginal communities. It now reads as follows:

“Significant heterogeneity exists between Aboriginal communities across the NT. The inclusion of data in our study from most, but not all, remote communities in the region could have introduced some bias and limit the generalisability. Furthermore, our findings may not be generalisable to Aboriginal peoples living in urban centres due to the unique environments and population characteristics of remote Aboriginal communities.”

The strengths and limitations summary statement on pg 3 has also been updated as follows:

> Our findings are unlikely to be generalisable to Aboriginal peoples living in urban centres or in ~~other regions of Australia~~.

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Reviewer: 3

Dr. Somchit Jaruratanasirikul, Prince Songkla Univ Comments to the Author:

This study is a retrospective cohort analysis describing the prevalence and burden of DM in among aboriginal people in remote communities of the Northern Territory, Australia (N=21 267). The diagnosis of DM was based on the data from hospital and primary care ICD-10 coding, prescription and biochemistry tests (HbA1c, plasma glucose) in 7 years (from 1 July 2012 to 30 June 2019). The diabetes incidence was assessed in aggregate over a three-year period (2016/17 to 2018/19). The prevalence of DM increased from 14.4% in 2012 to 17.0% in 2018 which was very high and increased with age (peak at 50s), mostly with type 2 (about 98%). The incidence rate in the total population in 2018/2019 was 7.9 per 1000 person-years with the peak incidence among 50-59 year-olds.

The authors hypothesized for this high prevalence rate of DM was from multiple factors such as the transitions in daily lifestyle among the aboriginal people, the epigenetic factors during pregnancy (intrauterine exposure to hyperglycaemia or maternal undernutrition). The future burden of this high prevalence of diabetes was also mentioned.

The strengths and limitations of the study are well stated.

The legends for figures and Tables are well described.

Response

We thank the reviewer for the positive feedback on our manuscript.

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Reviewer: 4

Dr. Julius Mwita, University of Botswana Comments to the Author:

Well written manuscript.

The study well described the increasing trend of the burden(prevalence) of diabetes in the studied population.

Response

Thank you for the positive feedback.

For the reason stated (small numbers), the calculation of incidence rate was limited to one period: 2016/17 - 2018/19. Given what is already described by the trend of prevalence of diabetes, I don't

think the calculated incidence rate add anything more. I would therefore describe the prevalence, and omit incidence.

Response

Thank you for this suggestion. We acknowledge that our inability to accurately assess trends limits the impact of our findings relating to diabetes incidence. Nevertheless, we believe that reporting on incidence is essential to being able to monitor the epidemiology of diabetes over the coming years. Many large epidemiological studies are unable to report on incidence due to a lack of longitudinal data. It is a particular strength of our study. The diabetes prevalence in a population is affected not just by new diagnoses, but also improved life expectancy and survival with the condition. To evaluate the efficacy of public health strategies intended to prevent diabetes, we believe it is important for epidemiological studies to report incidence. While we are unable to report on trends in incidence, we are keen to document in the literature the current incidence rate which future studies can compare to. Furthermore, we think presenting incidence rates by decade of life (Figure 4) and describing the cohort of people with incident diabetes is valuable. It is these findings that strongly demonstrate the young age of onset of type 2 diabetes among Aboriginal people in this context.

For a reference supporting the value of assessing diabetes incidence, we suggest the following systematic review published in the BMJ:

Magliano DJ et al. Trends in incidence of total or type 2 diabetes: systematic review. BMJ, 2019;

366:15003. https://doi.org/10.1136/bmj.l5003

Results: When median is used in a sentence, it would be reasonable to state that whatever is in the bracket is IQR for a reader to understand. `~~~For instance; "Median age at baseline was 22 (9-39) years, ..."

Response

Thank you for noting this omission. It has been corrected.

Results: For consistency, describe all the proportions with their 95% CI as seen in some sentences.

Response

Thank you for this recommendation. The second paragraph of the results has been amended to include the previously omitted 95% CI when describing the prevalence of diabetes between the regions of Central Australia and the Top End. These findings now read as follows:

“In 2018/19, diabetes was more prevalent across all ages in Central Australia (23.0%, 95% CI: 22.0%-

24.1%) than the Top End (14.5%, 95% CI: 13.9%-15.1%, p<0.001). When restricted to adults, the prevalence was 39.5% (95% CI: 37.9%-41.1%) in Central Australia compared to 24.2% (95% CI: 23.3%-25.1%) in the Top End (p<0.001).”

For summary statistics describing the cohort, we have continued to present n(%) without 95% CI, which is standard practice.

VERSION 2 – REVIEW

REVIEWER	Falster, Kathleen University of New South Wales, Centre for Big Data Research in Health
REVIEW RETURNED	24-Mar-2022

GENERAL COMMENTS	The revisions have nicely addressed the comments on the first version of the submitted paper.

REVIEWER	Mwita, Julius University of Botswana, Internal medicine
REVIEW RETURNED	21-Mar-2022

GENERAL COMMENTS	no more comments