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# Risk of tuberculosis among people with diabetes mellitus: an Australian nationwide cohort study

Claudia Caroline Dobler,[1,2] Jeffrey Ronald Flack,[3] Guy Barrington Marks[1,2]

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[1]Department of Respiratory and Environmental Epidemiology, Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia
[2]Department of Respiratory Medicine, Liverpool Hospital, Sydney, Australia
[3]Diabetes Centre, Bankstown-Lidcombe Hospital, Sydney, Australia

**Correspondence to**
Dr Claudia Caroline Dobler; cdobler@med.usyd.edu.au

## ABSTRACT

**Objective:** Previous studies that have found an increased risk for tuberculosis (TB) in people with diabetes mellitus (DM) have been conducted in segments of the population and have not adjusted for important potential confounders. We sought to determine the RR for TB in the presence of DM in a national population with data on confounding factors in order to inform the decision-making process about latent tuberculosis infection (LTBI) screening in people with diabetes.

**Design:** Whole population historical cohort study.

**Setting:** All Australian States and Territories with a mean TB incidence of 5.8/100 000.

**Participants:** Cases of TB in people with DM were identified by record linkage using the National Diabetes Services Scheme Database and TB notification databases for the years 2001–2006.

**Primary and secondary outcome measures:** Primary outcome was notified cases of TB. Secondary outcome was notified cases of culture-confirmed TB. RR of TB was estimated with adjustment for age, sex, TB incidence in country of birth and indigenous status.

**Results:** There were 6276 cases of active TB among 19 855 283 people living in Australia between 2001 and 2006. There were 271 (188 culture positive) cases of TB among 802 087 members of the DM cohort and 130 cases of TB among 273 023 people using insulin. The crude RR of TB was 1.78 (95% CI 1.17 to 2.73) in all people with DM and 2.16 (95% CI 1.19 to 3.93) in people with DM using insulin. The adjusted RRs were 1.48 (95% CI 1.04 to 2.10) and 2.27 (95% CI 1.41 to 3.66), respectively.

**Conclusions:** The presence of DM alone does not justify screening for LTBI. However, when combined with other risk factors for TB, the presence of DM may be sufficient to justify screening and treatment for LTBI.

## ARTICLE SUMMARY

### Article focus

- National, general population-based, historical cohort study to estimate the risk of tuberculosis (TB) among people with diabetes mellitus (DM).
- Adjustment for important potentially confounding risk factors including age, sex, indigenous status and TB incidence in country of birth.

### Key messages

- Overall, people with DM have a 1.5-fold increased risk of developing TB.
- The risk for TB is higher among people who are using insulin for DM.
- DM accounts for a small proportion of cases of TB in a low TB incidence setting.

### Strengths and limitations of this study

- The strengths of this study are the cohort design, the large population size, the general population base for the study cohort and the adjustment for important potential confounders, especially TB incidence in the country of birth.
- The study limitations are the unavailability of laboratory results to indicate if blood glucose levels were well or poorly controlled in people with DM and the inability to reliably distinguish between type 1 and type 2 DM in this data source.

## INTRODUCTION

Tuberculosis (TB) continues to be a major global health problem. It is estimated that one-third of the world's population have TB infection, and there are 9.4 million new cases of TB per year.[1] Major impairment of cell-mediated immunity, such as occurs in HIV infection, leads to a dramatic increase in the risk of developing TB.[2] A lesser degree of impairment of immune function, such as occurs in patients with rheumatic diseases who are on moderate-to-high dose steroid treatment, has also been found to be associated with an increased TB risk.[3] Diabetes mellitus (DM) is a common chronic disease associated with impaired immune function. Cohort and case control studies have shown an association between DM and TB.[4–9] With the rising prevalence of DM in countries where TB is endemic, there has been renewed interest in the question of whether DM increases the risk of active TB and thus could significantly add to the worldwide burden of disease.

A meta-analysis of cohort studies conducted in 2008 showed that DM was associated with an increased risk of TB (RR 3.11, 95% CI 2.27 to 4.26).[10] However, this finding was based on only three cohort studies, two of which were conducted in renal transplant recipients, who had another powerful cause of immunosuppression.[11 12] It did include one general population cohort study, conducted among South Korean civil servants, which identified an increased risk of TB among people with DM.[5] Findings from case–control studies were heterogeneous with ORs ranging from 1.16 to 7.83.[10] Most of these case–control studies did not measure or control adequately for potential major confounders.[10] Hence, the findings of these case–control studies may not be a valid reflection of the true risk of TB in association with DM. Another cohort study, also from East Asia but not included in the meta-analysis, found that DM was associated with a modest increase in the risk of active, culture-confirmed and pulmonary TB with adjusted HRs of 1.8, 1.9 and 1.9, respectively.[4] An English study published in 2010 found a twofold to threefold increased risk of TB among patients admitted to hospital because of diabetes.[9]

With the growing epidemic of obesity and DM worldwide and continued high prevalence of TB in low-income countries,[13 14] it is important to obtain further data on the RR of TB in DM. We conducted a national, general population historical cohort study to estimate the risk of TB among people with DM with adjustment for important potentially confounding risk factors.

## METHODS

### Setting and cohort

We conducted a national, general population historical cohort study among all 19.9 million residents of Australia, 802 087 (4.0%) of whom were registered with the National Diabetes Services Scheme (NDSS). Australia has a low incidence of TB (5.8 per 100 000 population) and 86% of all TB cases occur in overseas-born people.[15] All TB treatment is provided free of charge.

### Description of data sources and data linkage

#### National Diabetes Services Scheme

People with DM were identified using the NDSS Database. The NDSS is a subsidy scheme operated by Diabetes Australia for the Australian government. People who are registered with the NDSS can access a range of products including blood and urine testing strips, syringes, needles and insulin pump consumables at a concessional price. In order to register with the NDSS, an individual must receive certification of a diagnosis of DM and, if relevant, the need for insulin therapy, from a doctor or credentialed diabetes educator.[16] Access to diagnostic services is enhanced by the existence of a universal health insurance system which gives access to primary care and other health services free of charge or at low cost to all. People with all types of DM (type 1, type 2, gestational diabetes) are eligible for registration with the NDSS. Diabetes type is self-reported by the patients at the time of registration and confirmed by a health professional. We included all subjects into the analyses that were registered with the NDSS between January 2001 and December 2006 except those with gestational diabetes. Data on names, sex, state or territory of usual residence, date of birth, country of birth, indigenous status and insulin use were extracted and sent to the database manager who performed the data linkage (see below).

#### State and territory TB notification databases

Notification of TB is compulsory in Australia as this notification initiates public health investigation and action. All TB cases are collected at State and Territory level. We used the State and Territory TB notification databases to identify patients with TB. All subjects that were notified for active TB disease to one of the State or Territory TB notification databases between January 2001 and December 2006 were included in our analyses. Data on names, date of notification, date of birth, sex, country of birth, indigenous status and TB culture results were extracted for this analysis.

#### Data linkage

People with DM who had an episode of active TB were identified by record linkage using the NDSS Database and the State and Territory TB notification databases from January 2001 to December 2006. The linkage was performed at the Australian Institute of Health and Welfare (AIHW). From the two data sets, match files were created containing a unique record identifier, the data linkage items (surname, given names and date of birth) and the data linkage check items (sex, country of birth, state/territory of residence). From each of the original data sets, analysis files were created containing the unique record identifier and all the data fields required for analysis. Each of the analysis files was then linked to the match files, and the record identifiers were removed from these analysis files. The data linkage also allowed exclusion of duplicate data on the same patient. The data linkage protocol from the AIHW has been published online.[17]

#### Census data for the general population

Estimates for the distribution of age group, country of birth, sex and indigenous status in the general population were obtained from the Australian Bureau of Statistics based on census data for 2006.

#### Sample size and study power

The annual incidence of TB in Australia is 5.8/100 000. Hence, over 6 years, the expected cumulative incidence is 35/100 000. The study population is the entire population of Australia, that is, 20 million people. We estimated that there were 1 000 000 persons with diabetes. The study had 80% power to detect a RR of 1.16 or higher.

### Statistical analysis

Only cases of TB that were notified after DM was diagnosed were included. The follow-up period started from 1 January 2001 or the date of DM diagnosis, whichever was the later and continued until 31 December 2006 or the date of diagnosis of TB, whichever was the earlier. TB incidence rates were expressed per 100 000 person-years of follow-up with asymptotic 95% CIs.[18]

The RR of TB in patients with DM was estimated using a log-binomial model with correction for overdispersion to prevent underestimation of SEs due to heterogeneity in the data. The model was adjusted for TB incidence in country of birth, sex, age and indigenous status. Individual-level data on these potential confounders were available for the DM and TB cohorts. For the general population, aggregate population data for these covariates were obtained from the Australian Bureau of Statistics in the form of a contingency table containing population numbers cross-classified by all possible combinations of strata of the covariates listed above. Age was classified into 5-year age groups, and country of birth was aggregated to groupings of countries with a similar incidence of TB (<10, 10–24, 25–49, 50–99, 100–299 and ≥300/100 000) based on published WHO data.[19]

Population attributable fraction was estimated using the formula: $(Pe \times (RR - 1))/((Pe \times (RR - 1) + 1)$, where RR is the RR, estimated as above, and Pe is the proportion of the population exposed to the risk factor, that is, the prevalence of DM in the population.[20]

We performed planned sub-group analyses based on insulin treatment status and TB culture status. In addition, interactions between DM status and age, sex, indigenous status and TB incidence in country of birth were tested.

All statistical analyses were carried out using SAS Statistical Software (V.9.2) (SAS Institute).

### Ethical approval

The study protocol was approved by the Sydney South West Area Health Service Human Research Ethics Committee—Western Zone, the New South Wales Population & Health Services Research Ethics Committee, the AIHW Ethics Committee, the Queensland Health Research Ethics & Governance Unit, the Department of Human Services Victoria Research Governance, the Australian Capital Territory Health Human Research Ethics Committee, the Department of Health Western Australia Human Research Ethics Committee, the Tasmania Health and Medical Human Research Ethics Committee and the South Australia Department of Health Human Research Ethics Committee and the Northern Territory Human Research Ethics Committee. The requirement for written or verbal patients' consent for this data linkage study was waived by all of the above ethics committees because existing data sources were used.

## RESULTS

The study population comprised 19 855 283 residents of Australia, 802 087 (4%) of whom were registered with the NDSS including 273 023 (1.4%) with DM who were using insulin. Characteristics of the DM population, the general population, the TB population and the DM population with TB are shown in table 1. The percentage of Australian-born people was slightly higher in the DM population than in the general population (74% vs 71%), and more people came from an area with a TB incidence below 25/100 000 (92% vs 84%). The mean duration of follow-up was 4.6 years.

There were 6276 TB notifications (5.7/100 000/year, 95% CI 5.5 to 5.8) in Australia during the study period (table 2). There were 271 cases of TB among 802 087 members of the DM cohort (7.4/100 000/year, 95% CI 6.5 to 8.3). Of these, 188 (69%) were culture positive, which is similar to the 70% culture positive cases among all TB notifications. There were 130 TB notifications among 273 023 people using insulin (9.1/100 000/year, 95% CI 7.6 to 10.9).

The crude RR of TB was 1.78 (95% CI 1.17 to 2.73) in all people with DM and 2.16 (95% CI 1.19 to 3.93) in people with DM using insulin. In the multivariate analysis adjusted for age, TB incidence in country of birth, indigenous status and sex, the RR of TB was 1.48 (95% CI 1.04 to 2.10) in all people with DM and 2.27 (95% CI 1.41 to 3.66) in people using insulin (table 3). The estimates of RR were slightly higher when the analysis was limited to culture-confirmed cases of TB (table 3).

The RRs were not significantly modified by age group, indigenous status, sex or incidence in country of birth (all p values for interaction >0.25).

The population attributable fraction of DM for TB was 1.7%, based on a diabetes prevalence of 3.6%.[21]

## DISCUSSION

In this large, population-based cohort study conducted in 19.9 million residents of Australia with adjustment for important confounding factors, we found that, overall, people with DM have a 1.5-fold increased risk of developing TB. Those who are using insulin for DM have a greater risk. We also found that the population attributable fraction of DM for TB was very small.

The results of our study extend the findings of previous studies, which have also observed an increased risk for TB in patients with DM. A cohort study in Hong Kong, limited to people aged 65 years or more, found an adjusted HR (aHR) of 1.77 (95% CI 1.41 to 2.24) for active TB and an aHR of 1.91 (95% CI 1.45 to 2.52) for culture-confirmed TB among patients with DM.[4] However, this study found that people with diagnosed DM and with haemoglobin HbA1c <7% at enrolment were not at increased risk of TB (aHR 0.68, 95% CI 0.33 to 1.36). A Korean cohort study conducted in 790 000 civil servants found a RR of 3.47 (95% CI 2.98 to 4.03) for pulmonary TB in people with DM and a RR of 5.15 for culture-confirmed cases (95% CI 3.82 to 6.94).[5] In the Korean study, a diagnosis of DM was based solely on blood glucose levels. Thus, it did not include diabetic subjects who were euglycaemic at the time of screening.

**Table 1** Characteristics of the general population, the DM population, the TB population and the TB in DM population

| Variable | General population excluding people with diabetes (n=19 053 196) | DM population (n=802 087) | TB population (n=6276) | TB in DM population (n=271) |
|---|---|---|---|---|
| Gender, n (%) | | | | |
| Female | 9 669 609 (51) | 386 427 (48) | 3045 (49) | 122 (45) |
| Male | 9 383 587 (49) | 415 660 (52) | 3231 (51) | 149 (55) |
| Age group in years, n (%) | | | | |
| <15 | 3 931 189 (21) | 6024 (1) | 272 (4) | 0 |
| 15–34 | 5 341 173 (28) | 39 482 (5) | 2220 (35) | 10 (4) |
| 35–54 | 5 526 963 (29) | 173 391 (21) | 1729 (28) | 56 (21) |
| 55–74 | 3 199 578 (17) | 366 534 (46) | 1176 (19) | 123 (45) |
| ≥75 | 1 054 293 (6) | 216 656 (27) | 879 (14) | 82 (30) |
| Country of origin, n (%) | | | | |
| Australian born | 13 477 425 (71) | 595 518 (74) | 1212 (19) | 131 (48) |
| Born overseas | 4 209 464 (22) | 206 569 (26) | 5064 (81) | 140 (52) |
| Unknown | 1 366 307 (7) | 0 | 0 | 0 |
| Indigenous status, n (%) | | | | |
| Non-indigenous or not stated | 18 622 238 (98) | 780 197 (97) | 6072 (97) | 265 (98) |
| Indigenous | 430 958 (2) | 21 890 (3) | 204 (3) | 6 (2) |
| TB incidence in country of birth (per 100 000), n (%) | | | | |
| <25 | 16 052 757 (84) | 739 423 (92) | 1964 (31) | 168 (62) |
| 25–99 | 848 417 (4) | 36 292 (5) | 1350 (22) | 44 (16) |
| ≥100 | 728 119 (4) | 26 372 (3) | 2962 (47) | 59 (22) |
| Unknown | 1 423 903 (7) | 0 | 0 | 0 |

TB, tuberculosis.

In their systematic review on 13 observational studies on the risk of DM in TB, Jeon and Murray[10] found that studies which used laboratory testing as the basis for the diagnosis of DM had a higher RR for TB than those that used self-reporting or medical records (RR of 3.89, 2.26 and 1.61, respectively). If blood glucose levels are used for the definition of DM, patients with diabetes who have well-controlled glucose levels are less likely to be included. These findings imply that hyperglycaemia, rather than a DM diagnosis per se, increases the risk of developing active TB. This is supported by the observation by Leung *et al*[4] that patients with poor recent glycaemic control as evidenced by a haemoglobin HbA1c ≥7% had a significantly increased risk of TB (adjusted HR (aHR) 2.56, 95% CI 1.95 to 3.35), while those with a haemoglobin HbA1c <7% did not (aHR 0.81, 95% CI 0.44 to 1.48). In our study, DM diagnosis was based on self-reporting confirmed by a health professional, and laboratory results were not available. As insulin use is often a marker of longer duration and/or poorly controlled (type 2) DM, our finding that insulin users had a higher TB risk than the whole diabetes cohort

**Table 2** Crude incidence of TB in the general population and in people with diabetes

| | Incidence of all TB per 100 000/year (95% CI) | | Incidence of culture positive TB per 100 000/year (95% CI) | |
|---|---|---|---|---|
| | General population | People with diabetes | General population | People with diabetes |
| All persons | 5.7 (5.5 to 5.8) | 7.4 (6.5 to 8.3) | 4.0 (3.9 to 4.1) | 5.1 (4.4 to 5.9) |
| Age, years | | | | |
| <15 | 1.2 (1.1 to 1.4) | 0 | 0.4 (0.3 to 0.5) | 0 |
| 15–34 | 7.4 (7.1 to 7.7) | 6.1 (3.1 to 11.7) | 5.5 (5.2 to 5.8) | 4.3 (1.9 to 9.3) |
| 35–54 | 5.5 (5.2 to 5.7) | 7.5 (5.8 to 9.9) | 3.9 (3.7 to 4.1) | 5.5 (4.0 to 7.6) |
| 55–74 | 6.0 (5.6 to 6.3) | 7.4 (6.2 to 8.9) | 4.1 (3.8 to 4.4) | 4.9 (3.9 to 6.1) |
| ≥75 | 13.0 (12.1 to 13.9) | 7.5 (6.0 to 9.4) | 9.7 (9.0 to 10.5) | 5.4 (4.2 to 7.0) |
| Sex | | | | |
| Male | 5.9 (5.7 to 6.2) | 7.9 (6.7 to 9.3) | 4.3 (4.1 to 4.5) | 5.4 (4.4 to 6.6) |
| Female | 5.4 (5.2 to 5.6) | 6.9 (5.7 to 8.3) | 3.7 (3.6 to 4.9) | 4.9 (3.9 to 6.0) |
| TB incidence in country of birth | | | | |
| <25/100 000 | 1.95 (1.86 to 2.04) | 4.9 (4.2 to 5.7) | 1.26 (1.20 to 1.34) | 3.4 (2.8 to 4.1) |
| 25–99/100 000 | 25.5 (24.1 to 26.9) | 30.1 (22.1 to 40.8) | 18.0 (16.9 to 19.2) | 18.5 (12.4 to 27.3) |
| ≥100/100 000 | 65.4 (63.1 to 67.8) | 57.8 (44.4 to 75.0) | 48.8 (46.8 to 50.9) | 45.0 (33.3 to 60.6) |

TB, tuberculosis.

Table 3 RRs (crude and adjusted) for different TB end points

| Characteristics | Crude RR univariate analysis (95% CI) | p Value | Adjusted RR* multivariate analysis (95% CI) | p Value |
|---|---|---|---|---|
| All TB | 1.78 (1.17 to 2.73) | 0.008 | 1.48 (1.04 to 2.10) | 0.03 |
| Culture-positive TB | 1.83 (1.19 to 2.81) | 0.006 | 1.49 (1.05 to 2.11) | 0.02 |
| All TB in insulin users | 2.16 (1.19 to 3.93) | 0.01 | 2.27 (1.41 to 3.66) | 0.0008 |
| Culture-positive TB in insulin users | 2.44 (1.37 to 4.34) | 0.002 | 2.55 (1.62 to 4.01) | <0.001 |

*Adjusted for sex, age, indigenous status and TB incidence in country of birth.
TB, tuberculosis.

would support the assumption that hyperglycaemia increases the risk for developing active TB. However, as we did not have any data on duration of DM or HbA1C levels, and people with type I diabetes were included in the insulin-treated group, it remains unclear whether insulin use is an independent risk factor for TB or a proxy for longer duration or greater severity of DM.

Age did not modify the effect of DM on risk of TB in our study. Two published studies have demonstrated stronger associations of DM with TB among people aged less than 40 years compared with older people.[5 8] In these studies, the definition of DM cases was based on laboratory results. Another study, which had a DM diagnosis based on medical records, did not show the same trend for age.[22]

Interestingly, there is some evidence that the strength of the association of DM and TB increases with increasing background TB incidence in the study population.[7 10] This trend was found in a systematic review on the risk of TB in DM in 13 observational studies[10] and in a Texan study that found that the association was stronger for the population in the Texas border region, where there are higher incidence rates of TB, compared with non-border counties.[7] The reason for this observation is not entirely clear, but it could well relate to the level of glucose control in patients with DM in settings with a high TB incidence.

The strengths of our study are the cohort design, the large population size and the general population base for the study cohort. We believe that the diabetes cohort represents a virtually complete cohort of patients with diagnosed diabetes in Australia. The Australian Diabetes, Obesity and Lifestyle Study (1999–2000), which included previously undiagnosed cases identified by blood glucose estimations, estimated that 950 000 persons aged 25 years and over had diabetes.[23] The National Health Survey 2004–2005 found that 700 000 (3.6%) Australians identified themselves as having DM.[21] In the same period, 733 000 (3.6%) Australians with a certified diagnosis of DM were registered with the NDSS.[21] On the basis of these and other data, Diabetes Australia estimates that the NDSS covers 80%–90% of people with diagnosed DM.[21] The AIHW has identified the NDSS as one of the best available sources for monitoring the prevalence of diagnosed DM in Australia, based on coverage of the DM population, currency of the data source and frequency of updates to the data source.[21] However, we acknowledge that the findings of this study may not be generalisable to people with undiagnosed DM, who may have an elevated risk of TB compared with those truly without diabetes.

Ascertainment of cases of TB is likely to be complete. TB is a notifiable disease in Australia and notification by hospitals, doctors, TB clinics and pathology laboratories leads to public health action. The rate of undiagnosed TB in Australia is assumed to be very low as all investigations and treatment related to TB are provided free of charge for everybody, independent of insurance and immigration status, thus lowering the threshold to access care.

An additional strength of this study is the adjustment for important potential confounders, especially for the TB incidence in the country of birth. The incidence of TB in the country of birth is one of the strongest predictors of the risk of developing TB, but none of the previously published studies had adjusted the RR for this important confounder.[10] This adjustment is especially important for settings with a low incidence of TB, where the majority of TB cases usually occur in foreign-born people.[24] The adjustment for the incidence of TB in country of birth also makes the study results generalisable to populations with varying incidence of TB.

Our study has some limitations. As outlined above, laboratory results were not available to indicate if blood glucose levels were well or poorly controlled in people with DM. However, the diagnosis of DM in this study population is robust as all individuals registered with the NDSS must receive certification of a diagnosis of DM by a doctor or a credentialed diabetes educator. The available data did not allow us to reliably distinguish between type 1 and type 2 DM. It did allow us to reliably distinguish between patients treated with insulin and those not treated with insulin.

Although, as described above, we did adjust for potential confounding due to the major risk factors for TB in Australia, we did not have information on socioeconomic status, which may have been a confounding factor in this setting. A limitation that this study shares with previously published papers in this area is that we did not have any information on treatment of latent tuberculosis infection (LTBI) in the NDSS cohort. However, routine assessment and treatment for LTBI in patients with diabetes is currently not recommended in Australia, and it can therefore be assumed that most people with diabetes would not have been assessed and treated for LTBI.

## CONCLUSIONS

DM is associated with a modest increase in the risk of developing TB. The risk is greater among those treated with insulin for diabetes. Based on this modest RR, the presence of DM alone does not justify screening for, and treatment of, LTBI. However, when combined with other risk factors for TB, the presence of DM may be sufficient to justify screening and treatment for LTBI. The low population attributable risk, at least in Australia, suggests that control of TB in people with DM is unlikely to make a major contribution to the burden of TB in the population.

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**Contributors** All authors were involved in study concept and design, acquired data, revised the manuscript for important content and approved the final manuscript. CCD drafted the manuscript. GBM performed the statistical analysis.

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**Competing interests** None.

**Patient consent** The requirement for written or verbal patients consent for this data linkage study was waived by all of the above ethics committees because existing data sources were used.

**Ethics approval** The study protocol was approved by the Sydney South West Area Health Service Human Research Ethics Committee—Western Zone, the New South Wales Population & Health Services Research Ethics Committee, the Australian Institute of Health and Welfare Ethics Committee, the Queensland Health Research Ethics & Governance Unit, the Department of Human Services Victoria Research Governance, the Australian Capital Territory Health Human Research Ethics Committee, the Department of Health Western Australia Human Research Ethics Committee, the Tasmania Health and Medical Human Research Ethics Committee, the South Australia Department of Health Human Research Ethics Committee and the Northern Territory Human Research Ethics Committee.

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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 6 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 7 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7-9 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 7-9 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 9 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 9-10 |
| Bias | 9 | Describe any efforts to address potential sources of bias | |
| Study size | 10 | Explain how the study size was arrived at | 9 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 10 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 9-10 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 10 |
| | | (*c*) Explain how missing data were addressed | Data linkage, not clinical trial |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | NA |
| | | (*e*) Describe any sensitivity analyses | NA |

| | | | |
|---|---|---|---|
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | Data linkage, not clinical trial |
| | | (b) Give reasons for non-participation at each stage | See above |
| | | (c) Consider use of a flow diagram | See above |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 12+ Table1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | NA |
| | | (c) Summarise follow-up time (eg, average and total amount) | 12 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 12 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 12, Table 2+3 |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Table 2 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 12 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 14 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 14-17 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 16-17 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 18 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.