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# Excess mortality in early adulthood in a population-based cohort of childhood onset type 1 diabetes


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## BACKGROUND

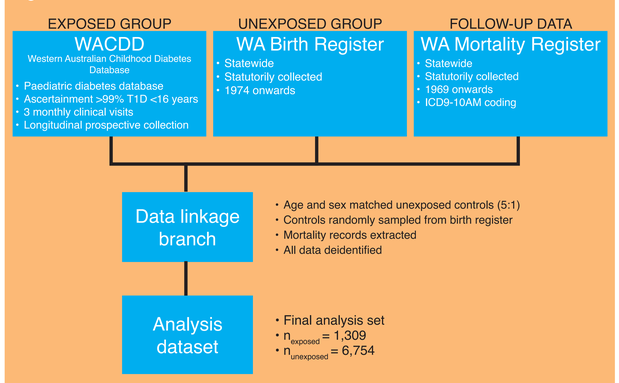
- Standardised Mortality Ratios (SMR) for death during early adulthood (<40 years) for patients with childhood-onset type 1 diabetes (T1D) vary between studies, with reports ranging from as low[1] as 2 through to as high[2] as 12. Differences may in part be due to differences in study design.
- Few mortality studies have included longitudinal clinical data. There is currently a paucity of data examining the relationship between childhood clinical measures and early adulthood mortality.
- A Danish study with longitudinal pathology data (4 years) found a strong association between glycaemic control and increased risk of all-cause mortality in patients with long standing T1D[3]. A hazard ratio of 1.47 (p<0.001) for an increase of 1% in mean glycated haemoglobin level ($HbA_{1c}$) was observed for all-cause mortality. This study (n=389) included patients of all ages and serves to highlight the importance of examining the association between clinical variables and mortality.

## AIMS

- To calculate standardised mortality ratios for death during early adulthood (<40 years) for those with childhood-onset type 1 diabetes relative to the general population.
- To examine the association between clinical and demographic risk factors (during childhood and adolescent management) with risk of death during early adulthood (<40 years).

## DATA LINKAGE

**Figure 1**




## METHODS AND RESULTS

### METHODS

**Data**

- All children in Western Australia (WA) (2012 population=2.4 million) with type 1 diabetes aged <16 years at diagnosis are treated by Princess Margaret Hospital for children. Clinical and demographic data from 3-monthly visits are stored in the WA Childhood Diabetes Database (WACDD).
- The WA Mortality Register (1969 onwards) was the source of mortality information. Cause of death is coded using the International Classification of Diseases (Versions 9, 9CM and 10AM). The WA Birth Register (1974 onwards) was used as the source for the unexposed group.

**Subjects**

- All patients with type 1 diabetes from the WACDD aged over 18 years of age as of 31 Dec 2011 were eligible for inclusion. This formed the exposed group. An age and sex matched (5:1) unexposed group was randomly sampled from the WA Birth Register.

**Statistical Analysis**

- Standardised mortality ratios (SMR) were calculated as per the indirect method. Cox proportional hazard models used to calculate hazard ratios (HR).

### RESULTS

**Standardised Mortality Ratio**

- In the exposed group (n=1,309) there were 20 deaths (8M/12F); in the unexposed group (n=6,754) there were 30 deaths (24M/6F). The SMR was 3.5 (95% CI; 2.2-5.8) for all subjects, 1.7 (95% CI; 0.9-3.5) for males and 10.4 (95% CI; 5.9-18.4) for females (**Table 1**).

**Cause of death**

- Causes of death, in decreasing order, among the exposed group were: an equal number 'other', accidental drug overdose and suicide, an equal number of CVD and 'diabetes related' deaths, followed by death from unexplained causes; among the unexposed group: suicide (11), motor vehicle accident (7), 'other' (6), accident, infection and accidental drug overdose.
- SMR was 20.77 (95% CI; 7.8,55.3; p<0.001) for accidental narcotic overdose. Other cause of death specific SMR's not estimated due to zero observations cells.

**Survival Analysis**

Adjusted HR from multivariate models presented in **Table 2**.

**Glycaemic control** (during paediatric management)

- HR for mean HbA1c (for a 1% increase in mean paediatric HbA1c) was 1.5 (95% CI; 1.1,2.1). The median longterm HbA1c for the 20 patients who died was 11.1% [IQR 9.7,12], min 8.4%.

**Socio-economic status** (at time of diagnosis)

- Relative to a those from a high level socio-economic background, those from a low and medium level socio-economic background were at increased risk, HR 6.2 (95% CI; 1.4,28.4) and 4.1 (95% CI; 0.9, 20.0) respectively, of death during early adulthood.

**Severe hypoglycamia** (during paediatric management)

- For severe hypoglycamia it was observed that there was no increased risk of mortality for those who experienced 1 or 2-3 episodes, while those who experienced 4 or more episodes had a HR of 3.8 (95% CI; 0.9,15.3), relative to those who experienced 0. This association was independent of duration of diabetes.

**Other factors**

- Glycaemic variability (HbA1c SD) and age of diagnosis were not significantly associated with increased risk of mortality.

### TABLES

**Table 1:** Standardised Mortality Ratios by age and sex for 1,309 cases of childhood-onset type 1 diabetes followed into early adulthood (<40 years)

| | Unexposed group (n=6,754) | | Exposed (T1D) group (n=1,309) | | T1D SMR | |
|---|---|---|---|---|---|---|
| Age group (years) | Person years observed | Mortality rate[a] | Person years observed | Mortality rate[a] | SMR | 95% CI |
| Men | | | | | | |
| 18-19 | 6,440 | 0.93 | 1,284 | 0.78 | 0.84 | (0.12,5.94) |
| 20-24 | 11,817 | 0.76 | 2,334 | 0.86 | 1.12 | (0.28,4.50) |
| 25-29 | 6,916 | 0.87 | 1,310 | 2.29 | 2.64 | (0.85,8.18) |
| 30-34 | 2,892 | 1.04 | 510 | 1.96 | 1.89 | (0.27,13.42) |
| 35-39 | 391 | 0.00 | 43 | 23.28 | 0.00 | - |
| Total | 28,455 | 0.84 | 5,481 | 1.46 | 1.73 | (0.87,3.46) |
| Women | | | | | | |
| 18-19 | 6,351 | 0.00 | 1,275 | 0.79 | 0.00 | - |
| 20-24 | 12,060 | 0.33 | 2,368 | 2.53 | 7.64 | (3.43,17.01) |
| 25-29 | 6,855 | 0.15 | 1,277 | 3.13 | 21.47 | (8.06,57.20) |
| 30-34 | 2,872 | 0.00 | 502 | 1.99 | 0.00 | - |
| 35-39 | 363 | 2.75 | 45 | 0.00 | 0.00 | - |
| Total | 28,503 | 0.21 | 5,467 | 2.20 | 10.43 | (5.92,18.36) |

[a] per 1,000 person-years

**Table 2:** Adjusted (year of birth and variable present in table) analyses of clinical and demographic risk factors with early adulthood (<40 years) all-cause mortality (n=1,272)[a]

| | HR[b] (95% CI) | P-value |
|---|---|---|
| Glycaemic control (mean HbA1c (%))[c] | 1.51 (1.1,2.1) | 0.012 |
| Total no. of severe hypoglycaemia episodes | | |
| 0 | 1 | N/A |
| 1 | 0.69 (0.1,5.5) | 0.722 |
| 2-3 | 0.98 (0.1,7.9) | 0.981 |
| 4+ | 3.78 (0.9,15.3) | 0.062 |
| Socio-economic background | | |
| Low | 6.21 (1.4,28.4) | 0.019 |
| Medium | 4.14 (0.9,20.0) | 0.076 |
| High | 1 | N/A |

[a] Reduced sample to account for missing socio-economic background data, this subset included 19 deaths
[b] Adjusted Hazard Ratio from a cox proportional hazard model additionally adjusted for birth year
[c] Mean HbA1c from all clinic visits

## CONCLUSION

- Females with childhood onset type 1 diabetes have a significantly higher mortality rate during early adulthood (<40 years) than the general population. Poor glycaemic control, low socio-economic status and a history of recurrent severe hypoglycaemia (4+ episodes) during paediatric management are associated with increased risk of mortality during early adulthood. The 25-29 year age group was the group with the highest risk of mortality relative to the general population.
- These findings may aid in identifying patient groups most at risk of early adulthood mortality allowing for primary patient care facilities to offer increased patient care. Increased patient care for this groups may be highly beneficial during the often difficult transition period from paediatric care to adult care facilities.

## REFERENCES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## RESULTS OVERVIEW

**1.7** 1.7 (95% CI 0.9-3.5). The SMR for males with T1D relative to the general population

**10.4** 10.4 (95% CI 5.9-18.4). The SMR for females with T1D relative to the general population

**1.5** 1.51 (95% CI 1.1-2.1) The hazard ratio for increased risk of all-cause mortality during early adulthood for every 1% (unit) increase in mean HbA1c during paediatric management

**6.2** 6.21 (95% CI 1.4-28.4) The hazard ratio for increased risk of all-cause mortality during early adulthood for those from a low relative to those from a high socio-economic background