Title

Spatial and temporal variation in Type 1 Diabetes incidence in Western Australia from 1991 to 2010: increased risk at higher latitudes and over time.

Abstract

This study analysed spatial and temporal variation in childhood incidence of Type 1 Diabetes Mellitus (T1DM) among Western Australia's 36 Health Districts from 1991 to 2010. There was a strong latitudinal gradient of 3.5% (95% CI, 0.2-7.2) increased risk of T1DM per degree south of the Equator, as averaged across the range 15° to 35° south. This pattern is consistent with the hypothesis of vitamin D deficiency at higher latitudes. In addition there was a 2.4% (95% CI, 1.3-3.6) average increase in T1DM incidence per year. These effects could not be explained by population density, socioeconomic status, remoteness or ethnicity.

Keywords

Type 1 Diabetes Mellitus; latitude; remoteness; socioeconomic status; population density; ethnicity

Introduction

The incidence of Type 1 Diabetes Mellitus (T1DM) among children is a growing health problem worldwide. While there have been significant gains in the management and prognosis of T1DM cases (Nathan et al., 2009), there has been a sustained increase of 2-5% per year in the incidence of T1DM throughout the world (Diamond Project Group, 2006; Onkamo et al., 1999). In addition, geographic variation in T1DM is among the largest observed for any non-communicable disease (Liese et al., 2010).

The aetiology of T1DM is complex and not yet well-understood (Atkinson and Eisenbarth, 2001). The established view is that multiple genetic and environmental factors are required to initiate the onset of T1DM (Akerblom and Knip, 1998; Atkinson and Eisenbarth, 2001; Gan et al., 2012), with environmental factors thought to include diet, vitamin D deficiency and exposure to infections.

Epidemiological studies have helped to identify potential environmental risk factors of T1DM (Akerblom et al., 2002). For example, spatiotemporal clusters of T1DM incidence might be explained by episodic infectious agents triggering disease onset (McNally et al., 2009; Samuelsson and Carstensen, 2003). Patterns of increased risk of T1DM at higher latitude have been interpreted in terms of reduced exposure to ultraviolet radiation leading to vitamin D deficiency (Mohr et al., 2008; Staples et al., 2003). Higher rates of T1DM in sparsely-populated areas could be explained by fewer opportunities for early childhood exposure to communicable infections which would otherwise promote the development of a more regulated immune system

(Cardwell et al., 2006; du Prel et al., 2007; Patterson et al., 1996; Waldhoer et al., 2008). Geographic associations between socioeconomic status and T1DM incidence may be attributable to spatial patterns in population composition, leading to differences in lifestyle, maternal age, diet and exposure to infections (du Prel et al., 2007; Patterson et al., 2001; Patterson and Waugh, 1992).

Efforts to identify plausible and predictable mechanisms for geographic risk factors of T1DM have been challenged by inconsistent results among studies. Whereas some studies show higher rates of T1DM in sparsely-populated rural areas than in urban areas (Cardwell et al., 2006; Holmqvist et al., 2008; Patterson and Waugh, 1992), other studies show the reverse pattern (Cherubini et al., 1999; Haynes et al., 2006) or no difference (Schober et al., 2003; Schoenle et al., 2001). Results for socioeconomic status are similarly diverse: high risk of T1DM has been variously associated with high socioeconomic status (Haynes et al., 2006; Patterson and Waugh, 1992; Siemiatycki et al., 1988; Tarn et al., 1983; Torres-Aviles et al., 2010), low socioeconomic status (Blom et al., 1989; Christau et al., 1977; Crow et al., 1991; Hungarian Childhood Diabetes Epidemiology Study Group, 1994; Waugh, 1986), or not at all (Bruno et al., 2000; Evans et al., 2000; Harron et al., 2011; Laporte et al., 1981).

Modelling multiple factors within individual studies is an important tool in resolving apparently inconsistent effects of risk factors. For example, urban-versus-rural differences in T1DM risk may be strongly correlated with socioeconomic patterns (Holmqvist et al., 2008; Patterson and Waugh, 1992). Thus, the multi-factorial nature of environmental contributors to T1DM requires a multi-factorial approach to

epidemiological studies; otherwise ongoing inconsistencies can be expected from the effects of unmeasured but correlated environmental or sociodemographic factors.

Beyond hidden effects within studies, the meaning of key variables is highly context-dependent. For example the meaning of remoteness as applied to Northern Ireland (Cardwell et al., 2006) with 1.7 million people within 14,135 km² in 2001 (Cardwell et al., 2007) is very different to the meaning of remoteness in Western Australia (Haynes et al., 2006) with 1.8 million people within 2,529,875 km² in 2001 (Edwards, 2003). The effect of socioeconomic status may also be highly context-dependent given that it probably acts as a proxy for a diverse set of more directly-acting mechanisms (Patterson and Waugh, 1992). Therefore, to better understand the epidemiology of T1DM, there is a need for more multi-factorial studies across a variety of locations.

Here, we simultaneously model socioeconomic status, population density, latitude, remoteness and ethnicity as risk factors for childhood T1DM incidence using a complete register of all childhood T1DM cases in Western Australia. Previous research in Western Australia showed a higher incidence of T1DM was associated with areas of high socioeconomic status, and urban areas rather than rural/remote areas, and that these associations were independent of each other (Haynes et al., 2006). A motivation for the current study was to examine spatial differences in T1DM in more detail, and to test additionally for the effects of latitude, population density and ethnicity. Western Australia has a highly centralised population, with three-quarters of the State's population within the Perth metropolitan area (Edwards,

2003). While the remaining population is sparse (total = 508,157 outside Perth at an average of 0.2 people per km² in 2001 (Edwards, 2003)), its broad latitudinal distribution (15° to 35° south) provides a valuable opportunity for examining an effect of latitude within a single diabetes data register. Given previous evidence of a strong temporal trend in the incidence of T1DM worldwide (Onkamo et al., 1999), we structure the analysis as a spatiotemporal model of T1DM incidence, using 20 years of data (1991-2010) to allow for temporal as well as spatial differences in socioeconomic status, population density, ethnicity and where children live in relation to latitude and remoteness. Finally, to measure spatiotemporal variation in T1DM incidence that is unexplained by these covariates, we add terms for spatial random effects and a temporal trend.

Methods

Setting

This study analysed spatial and temporal variation in the incidence of T1DM diagnosed in children aged less than 15 years among Western Australia's 36 Health Districts, from 1991 to 2010.

Data source and data structure

Cases of T1DM were sourced from the Western Australian Children's Diabetes Database. This is a diabetes register, maintained at Princess Margaret Hospital, of all known cases of T1DM diagnosed in Western Australia since 1985, with case ascertainment estimated at more than 99% from capture-recapture methods (Kelly et al., 1994). We identified cases as those patients diagnosed with T1DM who

commenced insulin therapy before 15 years of age. Patients with Type 2 diabetes or diabetes secondary to other causes such as cystic fibrosis and mature-onset diabetes of the young were excluded. The data were based on children diagnosed with T1DM between Jan 1st 1991 and Dec 31st 2010.

The data were aggregated within Western Australia's 36 Health Districts (Figure 1). We stratified the data by year of diagnosis, sex, and age group at diagnosis (0-4 years; 5-9 years; 10-14 years). The numbers of children at risk by Health District, sex and age group were obtained from the Australian Bureau of Statistics' national census data, based on five-yearly censuses: 1991, 1996, 2001, 2006 and 2011. Population sizes for the years between censuses were estimated by adjusting for annual births and deaths data (Rates Calculator software - Epidemiology Branch, Department of Health Western Australia, 2013). Denominators were based on non-Indigenous children, as T1DM is very rare among Indigenous children in Western Australia (Glatthaar et al., 1988). Throughout this paper we use the term Indigenous to refer collectively to people of Aboriginal and Torres Strait Islander descent. Only one of the 1571 cases of T1DM in the study was an Indigenous child. The identity of this record was not supplied for this study; therefore the record remained in the analysis. We assume this had a negligible impact on the results.

Covariates

We modelled socioeconomic status, population density, latitude, remoteness and ethnicity as covariates. Remoteness was assigned as urban, rural or remote as defined in 2005 by the Western Australian Department of Health (Figure 1). We committed to a static classification of remoteness over the 20-year study period, for

consistency with previous research (Haynes et al., 2006) which found differences in the incidence rate of Type 1 Diabetes between these same remoteness categories. The effects of any changes in remoteness that are not captured by this static classification may be partially captured by our inclusion of a variable for population density, and the inclusion of random effects (see below).

Socioeconomic status (SES) was based on the Australian Bureau of Statistics' Index of Socioeconomic Relative Disadvantage (IRSD) (Pink, 2008). This index, which is generated for each five-yearly national census, summarises a range of information relating to the economic and social conditions of people and households within areas (e.g. income, educational attainment and unemployment). The set of variables differs somewhat between censuses. In deriving the Index for each census, the Australian Bureau of Statistics use a Principal Components Analysis to assign each variable a weighting (Pink, 2008). Individual census areas are then given a score based on the sum of their variable weightings. For censuses prior to 2011 we assigned each Health District a population-weighted mean IRSD value based on component Census Collection Districts (assigned by their centroid locations). In urban areas, Census Collection Districts each contain approximately 250 households (Pink, 2008). There were 4370 Census Collection Districts in Western Australia in 2006 (Trewin, 2006). For the 2011 census we used the Australian Bureau of Statistics' new small-area category of Statistical Area 1 (n = 5512 in Western Australia) (Pink, 2011). Figure 2 shows examples of Census Collection Districts and Statistical Areas 1 in relation to Health Districts. Within each census, we ranked Health Districts to derive socioeconomic quintiles, and modelled this as a categorical variable. Socioeconomic quintiles for each census were assigned as follows: 1991-

1993 (1991 census); 1994-1998 (1996 census); 1999-2003 (2001 census); 2004-2008 (2006 census); 2009-2010 (2011 census).

Each Health District's population density was calculated as the median density (people per km²) based on the distribution of people among Census Collection Districts (or Statistical Areas 1 for the 2011 census) whose centroid was within the Health District in question. Thus, a Health District with a median population density of 1000 people per square kilometre refers to a District where 50% of people live within Census Collection Districts that contain at least 1000 people per km².

A population-weighted mean latitude was calculated for each Health District, based on the centroids of Census Collection Districts (or Statistical Areas 1 for the 2011 census), measured in decimal degrees south (Geocentric Datum of Australia 1994). Population-weighted latitude was calculated separately for each five-year census period to allow for changes in population distribution within each Health District.

We modelled ethnicity as the proportion of each Health District's non-Indigenous population that was of European descent, based on census data on country-of-birth (Australian Bureau of Statistics' Basic Community Profile data). These data were sourced at the level of Census Collection Districts (pre-2011 census) or Statistical Areas Level 1 (2011 census) and aggregated based on their centroid locations within Health Districts. We defined people of European descent as those born in Europe, in Australia (excluding Indigenous Australians), or in countries whose immigrants to Australia are typically of European ancestry (e.g. New Zealand and South Africa). Appendix 1 lists countries included by this definition. Given that people born in Asia

comprise a large proportion of the non-European immigrants to Australia (Appendix 1), and given the generally higher rates of Type 1 Diabetes in European countries relative to Asian countries (Karvonen et al., 1993), we have used the proportion of population of European descent to capture a likely ethnic difference in the risk of Type 1 Diabetes in Western Australia.

Statistical Methods

The incidence of T1DM was modelled as a Poisson-distributed rate:

$$R_{ij} \sim \text{Poisson}(\lambda_{ij})$$

where R_{ij} is the number of new T1DM cases in area i and year j . Poisson regression was used to model spatial and temporal variation in the incidence rate (λ). As a reference model, we initially ran a Null Model which assumed T1DM incidence was constant for all Districts and all years:

$$\log(\lambda_{ij}) = \log(e_{ij}) + \beta_0 \tag{1}$$

where e_{ij} is an offset term for population size, which also allows for the expected number of cases to be adjusted by age and sex. Thus, for each Health District in each year, e_{ij} is the expected number of T1DM cases based on (a) the number of children in each five-year age category (0-4 years; 5-9 years; 10-14 years) and each sex, and (b) the overall rates of T1DM per age-sex category across the dataset.

We added fixed effects to the Null Model to identify covariates which may explain spatial and temporal variation in the incidence of T1DM. We included

socioeconomic status, remoteness, population density, latitude and ethnicity as fixed effects terms ($\beta_1, \dots \beta_n$):

$$\log(\lambda_{ij}) = \log(e_{ij}) + \beta_0 + \beta_1 X_{ij1} + \dots + \beta_n X_{ijn} \quad (2)$$

Socioeconomic status and remoteness were modelled as categorical variables, while population density, latitude and ethnicity were modelled as continuous variables. We ran a univariate model for each of these variables, and a fully-adjusted model that included all variables.

To measure spatiotemporal variation in T1DM incidence that was unexplained by the covariates, we added spatial random effects and a temporal trend to the fully-adjusted model that included all covariates:

$$\log(\lambda_{ij}) = \log(e_{ij}) + \beta_0 + \beta_1 X_{ij1} + \dots + \beta_n X_{ijn} + (\beta_t + d_i)t_j + u_i + v_i \quad (3)$$

where u_i is a spatially-correlated random effect and v_i is a heterogeneous (spatially-uncorrelated) random effect. Together, u_i and v_i model how disease incidence of each area varies from its covariate-adjusted risk of T1DM. The constant β_t models a linear temporal trend in incidence, where t is time in years; and d_i is a spatially-correlated random effect which allows for the temporal trend of each area to vary from the mean temporal trend, following Bernardinelli (Bernardinelli et al., 1995). See Appendix 2 for model details. Random effects provide a way of estimating extra-Poisson variation in disease rates that are not otherwise captured by fixed effects. The presence of a strong random effect would therefore suggest that there

are other, unobserved effects causing differences in the rate of Type 1 Diabetes between Health Districts and/or over time. This situation may arise if important factors are excluded from a model, or if included factors are poorly specified.

Each model was run as a Bayesian analysis. Bayesian techniques have a proven ability to solve disease mapping problems through the use of Markov Chain Monte Carlo sampling methods (Lawson, 2001). We specified uninformative normal prior distributions ($\mu = 0$; $\sigma = 1000$) for each of $\beta_0, \beta_1, \dots, \beta_n$, and following Gelman (Gelman, 2006) we specified uninformative half-normal prior distributions ($\mu = 0$; $\sigma = 100$) for the standard deviation of each of the random effects u , v and d . We used WinBUGS 1.4 software (Lunn et al., 2000), which uses Markov Chain Monte Carlo sampling to generate posterior distributions. For each model we used a burn-in of 1000,000 iterations, with posterior distributions generated from an additional 1000,000 iterations, thinned to 1000 samples. Convergence was confirmed using the Geweke diagnostic (Geweke, 1992).

The Deviance Information Criterion (DIC) was calculated for each model (Best et al., 2005; Spiegelhalter et al., 2002). The DIC measures how well a model fits the data, while adding a penalty for extra parameters. A difference in DIC of at least 7 units between competing models was treated as strong support for the model with the lowest DIC (Best et al., 2005).

Maps were generated using ArcGIS Desktop 10.1.

Ethics

Ethics approval for this study was obtained from the Princess Margaret Hospital Ethics Committee and the Department of Health (Western Australia) Human Research Ethics Committee. Informed consent was obtained from all patients prior to their data being stored on the Western Australian Children's Diabetes Database.

Results

Spatial and temporal variation in T1DM incidence

Health Districts with the highest risk of T1DM were generally in the southwest of Western Australia, and lowest rates were in the State's north (Figure 1). Mean incidence across Western Australia over 1991-2010 among non-Indigenous children was 20.8 per 100,000 person years (95% CI, 19.8-21.8). The incidence of T1DM increased 1.8% per year (95% CI, 1.0-2.7) on average over this period (Figure 3).

Age and sex standardisation

The incidence rate for 0-4 year olds was approximately half that of 5-14 year olds (Table 1). There was very little difference in incidence rate between boys and girls. Health Districts had similar age distributions to each other based on 20-year totals of population at risk: generally 30-40% of children were 0-4 years old (Appendix 3)

Temporal variation in covariates

There were low levels of temporal variation in covariates relative to the variation between Health Districts (Appendix 3). Of the 36 Districts, 14 Districts had no net change in socioeconomic quintiles between 1991 and 2010, 14 changed by 1

quintile, 6 changed by 2 quintiles, and 2 changed by 3 quintiles. There were 23 Districts where the change in population density from 1991 to 2010 was less than 200 people per km² (NB: maximum population density of any Health District in the intervening period was 2493 people per km²). The most that a Health District varied in population-weighted latitude over the study period was 0.5 degrees, and there were 27 Districts whose population-weighted latitude varied less than 0.1 degrees. The proportion of people of European descent was above 90% for most Districts throughout the study period. In 1991, the populations of all Districts were at least 87% European by descent; by 2010 there were eight Districts below this level.

Fixed effects models

Latitude

Among the covariates examined, latitude provided the best fit to T1DM incidence data, with higher T1DM risk at latitudes further away from the Equator (Figure 4a; Table 2). The latitude-only model estimated a gradient of 4.7% (95% credible interval 2.0-7.8) increased risk per degree away from the Equator (a credible interval is the Bayesian analogue of a confidence interval, and is also abbreviated CI). This model was a large improvement over the Null Model of T1DM being fixed among Health Districts and over time (Δ DIC = -11.2). After allowing for socioeconomic status, population density, remoteness and ethnicity, the effect of latitude was estimated at 3.5% (95% CI 0.2-7.2) per degree away from the Equator. NB: each degree of latitude is equivalent to approximately 111kms.

Remoteness

Remoteness provided a better fit to the data relative to the Null Model ($\Delta\text{DIC} = -5.8$). The risk of T1DM was highest in urban Health Districts and lowest in remote Districts (Figure 4b; Table 2). Without adjusting for the effects of socioeconomic status, population density, latitude and ethnicity, the rate of T1DM in remote areas was significantly lower than in urban areas: incidence rate ratio = 0.70 (95% CI, 0.55-0.88). However, the difference between remote and urban areas was not significant after adjusting for these other covariates: incidence rate ratio for remote areas = 0.80 (95% CI, 0.58-1.13).

Socioeconomic status

There was weak evidence of a socioeconomic effect. In the socioeconomic-only model and fully-adjusted model, the risk of T1DM was slightly higher for the two highest socioeconomic quintiles (Figure 4c; Table 2). There was large overlap among 95% credible intervals of socioeconomic quintiles, and adding socioeconomic status to the Null Model did not improve the level of model fit ($\Delta\text{DIC} = +4.9$).

Population density

Population density was a poor predictor of T1DM risk. In the density-only model, the incidence rate ratio of T1DM per population density increase of 100 people per km² was estimated at 1.004 (95% CI, 0.996-1.011) (Figure 4d; Table 2) and remained non-significant after adjustment for socioeconomic status, latitude, remoteness and ethnicity. Adding population density to the Null Model did not improve the level of model fit ($\Delta\text{DIC} = +0.9$).

Ethnicity

While the ethnicity-only model and fully-adjusted model both estimated higher risk of T1DM among Europeans, the 95% credible intervals for these estimates overlapped a null effect (Table 2). Adding ethnicity to the Null Model did not improve the level of model fit ($\Delta\text{DIC} = +1.9$). In the fully-adjusted model that also included a temporal trend and spatial random effects, there was a significant effect of ethnicity, equivalent to a notionally all-European District having a risk of T1DM 13.29 (95% CI 1.98-132.82) times that of a notionally non-European District.

Residual spatiotemporal variation

Adding spatial random effects and a temporal trend to the fully-adjusted model gave a large improvement in model fit ($\Delta\text{DIC} = -12.6$), and temporal trend was estimated as an incidence risk ratio of 1.024 (95% CI, 1.013-1.036) per year (Table 2). This model estimated very little variation among Health Districts in the temporal trend in T1DM incidence, and low levels of residual spatial variation in T1DM risk (Table 2).

Discussion

This study strengthens the case for taking a multi-factorial approach to the analysis of spatiotemporal variation in T1DM. Whereas previous research identified higher rates of T1DM within urban versus rural and remote Western Australia, here, by analysing the data at the finer spatial scale of the State's 36 Health Districts, and simultaneously controlling for remoteness, socioeconomic status, population density and ethnicity, we have isolated a previously unobserved latitudinal effect.

We found a strong latitudinal gradient in the risk of T1DM, with risk increasing 3.5% per degree of latitude away from Equator. This equates to a doubling of risk across Western Australia's latitudinal range (15° to 35° south). A limitation of this study was that there were few Health Districts at low latitudes (nearer the Equator). Therefore, the observed effect may be strongly leveraged by a small fraction of the population. However, our results are consistent with other studies of T1DM in relation to latitude. Latitudinal gradients of increased T1DM risk away from the Equator have been observed between capital cities of Australia (Staples et al., 2003), within other countries (Yang et al., 1998), and between countries (Mohr et al., 2008; Patterson et al., 2001). Our study adds to previous research by demonstrating a latitudinal gradient at the scale of districts within a single large state, independent of area-level socioeconomic status, population density, remoteness and ethnicity.

Our results are consistent with the hypothesis that increased exposure to ultraviolet radiation at low latitudes (closer to the Equator) is protective against T1DM via an impact on vitamin D levels (Mohr et al., 2008; Staples et al., 2003). Key elements of this hypothesis are that (a) the risk of T1DM is reduced by immunomodulatory effects of vitamin D metabolites (Mohr et al., 2008), (b) that exposure to sunlight is responsible for a large part of circulating vitamin D and its metabolites (Adams et al., 1982), and (c) that vitamin D levels in children are considered to be commonly below clinical guidelines (Paxton et al., 2013). The plausibility of this hypothesis for our study population is strengthened by the association between latitude and clear-sky estimates of ultraviolet radiation in Western Australia (Figure 5). However, personal exposure to ultraviolet radiation will depend on patterns of childhood behaviour (e.g. day time activity) and the amount of ultraviolet radiation that penetrates cloud cover.

While we were unable to source such data, the latitudinal gradient observed in this study helps justify more detailed testing of the association between the incidence of T1DM, early-life exposure to ultraviolet radiation, and early-life vitamin D levels in this population.

This study showed that a difference in T1DM risk between urban, rural and remote Western Australia is partially explained by other variables. A logical candidate for this confounding is latitude, given the strong latitudinal gradient in T1DM risk, and the location of all 13 urban Health Districts near the southern limit of Western Australia.

There was very little difference in T1DM risk between levels of socioeconomic status. In the socioeconomic-only model the risk of T1DM was 16% higher in the least disadvantaged socioeconomic quintile than in the most disadvantaged quintile. This difference was similar in the fully-adjusted model. These results are in the same direction (higher risk for higher socioeconomic status), but of smaller magnitude than reported previously in Western Australia where the risk of T1DM in the least disadvantaged socioeconomic quintile was found to be 56% higher than in the most disadvantaged quintile (Haynes et al., 2006). The small effect of socioeconomic status observed in the current study may be an artefact of spatial averaging of socioeconomic diversity within each of the 36 Health Districts, given that Haynes et al. assigned socioeconomic status at the much smaller area scale of Census Collection Districts. As with any ecological study, observed patterns may depend on the scale of aggregation.

This study found no evidence for an association between population density and the risk of T1DM. Regardless of adjustment for covariates, the estimated effect of population density was negligible. These results are unexpected, given evidence elsewhere of an association between population density and the risk of T1DM, and the plausible explanation that high population density modifies the risk of developing T1DM by increasing exposure to pathogens (Patterson et al., 1996; Waldhoer et al., 2008). It seems unlikely that the small effect of population density was due to spatial averaging within Health Districts, as there was a broad range of population densities among Health Districts. Instead, we propose that if there is an effect of population density on T1DM through an impact on disease transmission rates, that effect may disappear when other aspect of human geography dominate patterns of disease transmission. Western Australia is highly unusual in this regard. Three quarters of the State's population live within the capital city Perth (Edwards, 2003) and much of regional Western Australia is isolated by vast distances. The nearest major city to Perth is Adelaide, more than 2000 kilometres away. This presents a situation where Western Australia's human geography may be dominated by a single location for the introduction and transmission of communicable diseases. In this context, differences in population density across Western Australia may have minimal effect on T1DM relative to other geographic factors.

Ethnicity added very little to predicting the spatiotemporal variation in T1DM incidence between Health Districts. While the direction of the estimated effects of ethnicity were consistent with our prediction that people of European descent would have relatively higher rates of T1DM (Karvonen et al., 1993), these estimates were statistically unstable. This instability is likely due to Europeans consistently making

up a very high proportion of the populations of most Health District populations (i.e. very little range in this exposure variable). Therefore, at the level of Health Districts we are unable to make strong conclusions about ethnic differences in T1DM risk in Western Australia. While this does not preclude there being important differences at the individual level, this District-level consistency does help to exclude ethnicity, as measured here, as a confounder of the other variables in this study.

While latitude was the main predictor of variation among Health Districts in the risk of T1DM, we found evidence of a strong residual temporal trend of T1DM incidence increasing by an average of 2.4% per year. Similar rates of increase in T1DM incidence have been reported around the world (Diamond Project Group, 2006; Onkamo et al., 1999). Suggested mechanisms include changes in early life diet, increased exposure to specific pathogens capable of triggering T1DM, decreased exposure to common pathogens in early childhood, and decreased vitamin D levels due to a reduction in outdoor activity (Vehik and Dabelea, 2011) and increasing use of protective clothing and sunscreen (Dobbinson et al., 2008). Our study found no evidence that the temporal trend in T1DM incidence varied spatially across Western Australia. This suggests that the set of mechanisms responsible for increased incidence of T1DM in Western Australia apply evenly across the landscape.

There are several limitations to our study. By summarising data at the scale of Health Districts we have forgone information at a finer spatial scale. It is important to keep in mind that all our conclusions are at the scale of Western Australia's Health Districts, and that some patterns may be hidden by the aggregation of data. Our analyses are based on time at diagnosis. Previous research has successfully shown

spatial and temporal patterns in T1DM incidence in relation to the timing and location of births rather than diagnosis (Samuelsson and Carstensen, 2003). Given that location at birth could more strongly reflect processes important in early life risk factors of T1DM, we flag this as a potential improvement on our study.

The strength of this study is that we have applied spatiotemporal modelling techniques to a high quality dataset on T1DM incidence which spans a broad geographic region over 20 years. By analysing variation in T1DM incidence at the scale of Western Australia's Health Districts we have observed a strong latitudinal effect of T1DM risk increasing away from the Equator, which is independent of socioeconomic status, population density, remoteness and ethnicity. Patterns of residual variation show a strong increase in T1DM incidence over time after taking these covariates into account.

Conclusions

T1DM follows a strong latitudinal gradient in Western Australia of increasing risk away from the Equator, and increasing risk over time; these trends could not be explained by population density, socioeconomic status, remoteness or ethnicity.

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Tables

Table 1. Total cases, person years of risk and mean incidence of childhood T1DM by age and sex in Western Australia from 1991 to 2010 among non-Indigenous children.

age group	sex	cases	person-years-at-risk	incidence per 100,000 (95% CI)
0-4 years	male	164	1,255,057	13.1 (11.1-15.2)
	female	144	1,188,721	12.1 (10.2-14.3)
5-9 years	male	291	1,296,251	22.4 (19.9-25.2)
	female	314	1,224,436	25.6 (22.9-28.6)
10-14 years	male	359	1,340,748	26.8 (24.1-29.7)
	female	299	1,260,822	23.7 (21.1-26.6)

Table 2. Effect sizes (with 95% credibility intervals) estimated from Poisson regression models of T1DM incidence.

Effect	Unadjusted fixed effect models	Adjusted fixed effects model ^a	Adjusted mixed model (fixed + random effects)
Latitude			
IRR ^b per degree south	1.047 (1.020-1.078)	1.035 (1.002-1.072)	1.037 (0.996-1.087)
Remoteness			
IRR Remote	0.699 (0.553-0.881)	0.804 (0.579-1.128)	0.770 (0.504-1.169)
IRR Rural	0.944 (0.829-1.079)	0.867 (0.701-1.065)	0.913 (0.656-1.157)
IRR Urban ^c	1.00	1.00	1.00
Socioeconomic status^d			
IRR SES 1	0.905 (0.730-1.150)	0.940 (0.758-1.180)	1.018 (0.786-1.285)
IRR SES 2	1.004 (0.830-1.199)	1.058 (0.885-1.294)	1.109 (0.911-1.333)
IRR SES 3 ^c	1.00	1.00	1.00
IRR SES 4	1.084 (0.938-1.265)	1.108 (0.950-1.305)	1.176 (0.981-1.398)
IRR SES 5	1.060 (0.931-1.227)	1.077 (0.935-1.238)	1.100 (0.892-1.309)
Population density			
IRR per 100 people per km ²	1.004 (0.996-1.011)	1.001 (0.987-1.015)	1.008 (0.992-1.029)
Ethnicity			
IRR %European	1.214 (0.456-3.225)	3.35 (0.767-16.593)	13.29 (1.979-132.821)
Time			
IRR per year	1.018 (1.008-1.025)		1.024 (1.013-1.036)
Random effects^e			
IQ range (IRR($u+v$))			0.987-1.013
IQ range (IRR(d))			0.999-1.001

^a Adjusted fixed effects model includes latitude, remoteness, socioeconomic status, population density and ethnicity as covariates, but not time.

^b IRR = incidence rate ratio.

^c Reference category.

^d Socioeconomic status is reported as quintiles (most deprived areas = SES 1; least deprived areas = SES 5).

^e Random effects are summarised here as the interquartile range of the incidence rate ratio among 36 Health Districts for $u+v$ (sum of spatially-correlated and spatially-uncorrelated random effects) and d (random effect that allows for a spatially-variable temporal trend in T1DM incidence).

Figure captions

Figure 1. Map of T1DM incidence in Western Australia, 1991-2010. This shows quintiles of the raw incidence rate among non-Indigenous children in 36 Health Districts. The location of each Health District label (numbers 1-36) indicates the approximate position of its population-weighted centroid (NB: these codes are used for cross-referencing with Appendix 3). Inset map shows the 13 urban Health Districts surrounding the capital city, Perth. Thick black lines indicate boundaries between urban, rural and remote regions.

Figure 2. Health District geography in relation to Australian Bureau of Statistics' census geography. These example areas show Health District boundaries (black lines) in relation to the census geography units (grey lines) used in this study.

Health Districts in urban Perth,
with Census Collection Districts from 2001 census

Health Districts in southwest of Western Australia,
with Census Collection Districts from 2001 census

Health Districts in urban Perth,
with Statistical Areas Level 1 from 2011 census

Health Districts in southwest of Western Australia,
with Statistical Areas Level 1 from 2011 census

Figure 3. Temporal trend in the annual incidence of T1DM among non-Indigenous children in Western Australia from 1991 to 2010. Incidence is indicated as the number of new cases diagnosed per 100,000 children at risk, unadjusted for age and sex ($\pm 95\%$ confidence intervals represented by vertical bars). The dashed line shows best-fit Poisson regression (first-order polynomial), which has an incidence rate ratio of 1.018 per year (95% CI: 1.010-1.027).

Figure 4. Mean incidence of childhood T1DM (cases per 100,000 person years at risk, $\pm 95\%$ confidence intervals) as a function of (a) latitude, (b) remoteness, (c) socioeconomic status (most deprived = 1; least deprived = 5), (d) population density and (e) ethnicity (proportion of population of European descent). Some confidence intervals for latitude, population density and ethnicity extend above the range shown. These rates were based on univariate analyses of data aggregated over 20 years, without standardising by age and sex. X-axis values for latitude, population density and ethnicity are 20-year medians for each of the 36 Health Districts.

Figure 5. Spatial variation in ultraviolet radiation (shaded bands) across Western Australia in relation to latitude (dashed lines). Numbers in bold indicate the average annual noon clear sky Ultraviolet Index over the period 1979-2007. UV data sourced from the Australian Bureau of Meteorology:

(http://www.bom.gov.au/jsp/ncc/climate_averages/uv-index/index.jsp?period=an#maps)

References

- Adams, J.S., Clemens, T.L., Parrish, J.A., Holick, M.F., 1982. Vitamin-D synthesis and metabolism after ultraviolet irradiation of normal and vitamin-D-deficient subjects. *New England Journal of Medicine* 306, 722-725.
- Akerblom, H.K., Knip, M., 1998. Putative environmental factors in Type 1 diabetes. *Diabetes-Metabolism Reviews* 14, 31-67.
- Akerblom, H.K., Vaarala, O., Hyoty, H., Ilonen, J., Knip, M., 2002. Environmental factors in the etiology of type 1 diabetes. *American Journal of Medical Genetics* 115, 18-29.
- Atkinson, M.A., Eisenbarth, G.S., 2001. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet* 358, 221-229.
- Bernardinelli, L., Clayton, D., Pascutto, C., Montomoli, C., Ghislandi, M., Songini, M., 1995. Bayesian analysis of space-time variation in disease risk. *Statistics in Medicine* 14, 2433-2443.
- Besag, J., York, J., Mollie, A., 1991. Bayesian image-restoration, with two applications in spatial statistics. *Annals of the Institute of Statistical Mathematics* 43, 1-20.
- Best, N., Richardson, S., Thomson, A., 2005. A comparison of Bayesian spatial models for disease mapping. *Statistical Methods in Medical Research* 14, 35-59.
- Blom, L., Dahlquist, G., Nystrom, L., Sandstrom, A., Wall, S., 1989. The Swedish childhood diabetes study - social and perinatal determinants for diabetes in childhood. *Diabetologia* 32, 7-13.
- Bruno, G., Pagano, G., Faggiano, F., De Salvia, A., Merletti, F., 2000. Effect of Sardinian heritage on risk and age at onset of type 1 diabetes: a demographic case-control study of Sardinian migrants. *International Journal of Epidemiology* 29, 532-535.
- Cardwell, C.R., Carson, D.J., Patterson, C.C., 2006. Higher incidence of childhood-onset type 1 diabetes mellitus in remote areas: a UK regional small-area analysis. *Diabetologia* 49, 2074-2077.
- Cardwell, C.R., Carson, D.J., Patterson, C.C., 2007. Secular trends, disease maps and ecological analyses of the incidence of childhood onset type 1 diabetes in Northern Ireland, 1989-2003. *Diabetic Medicine* 24, 289-295.
- Cherubini, V., Carle, F., Gesuita, R., Iannilli, A., Tuomilehto, J., Prisco, F., Iafusco, D., Altobelli, E., Chiarelli, F., De Giorgi, G., Falorni, A., 1999. Large incidence variation of Type I diabetes in central-southern Italy 1990-1995: lower risk in rural areas. *Diabetologia* 42, 789-792.
- Christau, B., Kromann, H., Andersen, O.O., Christy, M., Buschard, K., Arnung, K., Kristensen, I.H., Peitersen, B., Steinrud, J., Nerup, J., 1977. Incidence, seasonal and geographical patterns of juvenile-onset insulin-dependent diabetes mellitus in Denmark. *Diabetologia* 13, 281-284.
- Crow, Y.J., Alberti, K., Parkin, J.M., 1991. Insulin-dependent diabetes in childhood and material deprivation in Northern England, 1977-86. *British Medical Journal* 303, 158-160.
- Diamond Project Group, 2006. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. *Diabetic Medicine* 23, 857-866.
- Dobbinson, S.J., Wakefield, M.A., Jansen, K.M., Herd, N.L., Spittal, M.J., Lipscomb, J.E., Hill, D.J., 2008. Weekend sun protection and sunburn in Australia: Trends (1987-2002) and association with SunSmart television advertising. *American Journal of Preventive Medicine* 34, 94-101.

- du Prel, J.B., Icks, A., Grabert, M., Holl, R.W., Giani, G., Rosenbauer, J., 2007. Socioeconomic conditions and type 1 diabetes in childhood in North Rhine-Westphalia, Germany. *Diabetologia* 50, 720-728.
- Edwards, R.W., 2003. 2035.0 Census of Population and Housing, Population Growth and Distribution, Australia, 2001. Australian Bureau of Statistics.
- Evans, J.M.M., Newton, R.W., Ruta, D.A., MacDonald, T.M., Morris, A.D., 2000. Socio-economic status, obesity and prevalence of Type 1 and Type 2 diabetes mellitus. *Diabetic Medicine* 17, 478-480.
- Gan, M.J., Albanese-O'Neill, A., Haller, M.J., 2012. Type 1 Diabetes: Current Concepts in Epidemiology, Pathophysiology, Clinical Care, and Research. *Current Problems in Pediatric and Adolescent Health Care* 42, 269-291.
- Gelman, A., 2006. Prior distributions for variance parameters in hierarchical models. *Bayesian Analysis* 1, 515-533.
- Geweke, J., 1992. Evaluating the accuracy of sampling-based approaches to the calculation of posterior moments, in: Bernardo JM, B.J., Dawid AP, Smith AFM (Ed.), *Bayesian Statistics 4*. Oxford University Press, Oxford, pp. 169-193.
- Glatthaar, C., Whittall, D.E., Welborn, T.A., Gibson, M.J., Brooks, B.H., Ryan, M.M.P., Byrne, G.C., 1988. Diabetes in Western Australian children - descriptive epidemiology. *Medical Journal of Australia* 148, 117-123.
- Harron, K.L., McKinney, P.A., Feltbower, R.G., Bodansky, H.J., Norman, P.D., Campbell, F.M., Parslow, R.C., 2011. Incidence rate trends in childhood Type 1 diabetes in Yorkshire, UK 1978-2007: effects of deprivation and age at diagnosis in the south Asian and non-south Asian populations. *Diabetic Medicine* 28, 1508-1513.
- Haynes, A., Bulsara, M.K., Bower, C., Codde, J.P., Jones, T.W., Davis, E.A., 2006. Independent effects of socioeconomic status and place of residence on the incidence of childhood type 1 diabetes in Western Australia. *Pediatric Diabetes* 7, 94-100.
- Holmqvist, B.M., Lofman, O., Samuelsson, U., 2008. A low incidence of Type 1 diabetes between 1977 and 2001 in south-eastern Sweden in areas with high population density and which are more deprived. *Diabetic Medicine* 25, 255-260.
- Hungarian Childhood Diabetes Epidemiology Study Group, 1994. Non-genetic risk determinants for Type 1 (insulin dependent) diabetes mellitus in childhood. *Acta Paediatrica* 83, 730-735.
- Karvonen, M., Tuomilehto, J., Libman, I., Laporte, R., 1993. A review of the recent epidemiological data on the worldwide incidence of Type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 36, 883-892.
- Kelly, H.A., Russell, M.T., Jones, T.W., Byrne, G.C., 1994. Dramatic increase in incidence of insulin-dependent diabetes mellitus in Western Australia. *Medical Journal of Australia* 161, 426-429.
- Laporte, R.E., Orchard, T.J., Kuller, L.H., Wagener, D.K., Drash, A.L., Schneider, B.B., Fishbein, H.A., 1981. The Pittsburgh Insulin Dependent Diabetes Mellitus Registry - the relationship of insulin dependent diabetes mellitus incidence to social class. *American Journal of Epidemiology* 114, 379-384.
- Lawson, A.B., 2001. Disease map reconstruction. *Statistics in Medicine* 20, 2183-2204.
- Liese, A.D., Lawson, A., Song, H.-R., Hibbert, J.D., Porter, D.E., Nichols, M., Lamichhane, A.P., Dabelea, D., Mayer-Davis, E.J., Standiford, D., Liu, L., Hamman, R.F., D'Agostino, R.B., Jr., 2010. Evaluating geographic variation in type 1 and type 2 diabetes mellitus incidence in youth in four US regions. *Health & Place* 16, 547-556.
- Lunn, D.J., Thomas, A., Best, N., Spiegelhalter, D., 2000. WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility. *Statistics and Computing* 10, 325-337.

- McNally, R.J.Q., Pollock, R., Court, S., Begon, M., Cheetham, T.D., 2009. Space-time clustering analyses of type 1 diabetes in children from north-east England: support for an infectious aetiology? *Environmental Health* 8.
- Mohr, S.B., Garland, C.F., Gorham, E.D., Garland, F.C., 2008. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. *Diabetologia* 51, 1391-1398.
- Nathan, D.M., Zinman, B., Cleary, P.A., Backlund, J.-Y.C., Genuth, S., Miller, R., Orchard, T.J., Grp, D.E.R., 2009. Modern-Day Clinical Course of Type 1 Diabetes Mellitus After 30 Years' Duration The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983-2005). *Archives of Internal Medicine* 169, 1307-1316.
- Onkamo, P., Vaananen, S., Karvonen, M., Tuomilehto, J., 1999. Worldwide increase in incidence of Type I diabetes - the analysis of the data on published incidence trends. *Diabetologia* 42, 1395-1403.
- Patterson, C.C., Carson, D.J., Hadden, D.R., 1996. Epidemiology of childhood IDDM in Northern Ireland 1989-1994: Low incidence in areas with highest population density and most household crowding. *Diabetologia* 39, 1063-1069.
- Patterson, C.C., Dahlquist, G., Soltesz, G., Green, A., Grp, E.A.S., 2001. Is childhood-onset Type I diabetes a wealth-related disease? An ecological analysis of European incidence rates. *Diabetologia* 44, B9-B16.
- Patterson, C.C., Waugh, N.R., 1992. Urban/rural and deprivation differences in incidence and clustering of childhood diabetes in Scotland. *International Journal of Epidemiology* 21, 108-117.
- Paxton, G.A., Teale, G.R., Nowson, C.A., Mason, R.S., McGrath, J.J., Thompson, M.J., Siafarikas, A., Rodda, C.P., Munns, C.F., 2013. Vitamin D and health in pregnancy, infants, children and adolescents in Australia and New Zealand: a position statement. *Medical Journal of Australia* 198, 142-143.
- Pink, B., 2008. 2039.0 Information Paper: An Introduction to Socio-Economic Indexes for Areas (SEIFA), 2006.
- Pink, B., 2011. 1270.0.55.001 Australian Bureau of Statistics. Australian Statistical Geography Standard (ASGS): Volume 1 - Main Structure and Greater Capital City Statistical Area.
- Samuelsson, U., Carstensen, J., 2003. Space-time clustering at birth and at diagnosis of type 1 diabetes mellitus in relation to early clinical manifestation. *Journal of Pediatric Endocrinology and Metabolism* 16, 859-867.
- Schober, E., Rami, B., Waldhoer, T., Austrian Diabet Incidence Study, G., 2003. Small area variation in childhood diabetes mellitus in Austria: links to population density, 1989 to 1999. *Journal of Clinical Epidemiology* 56, 269-273.
- Schoenle, E.J., Lang-Muritano, M., Gschwend, S., Laimbacher, J., Mullis, P.E., Torresani, T., Bion-Laubert, A., Molinari, L., 2001. Epidemiology of Type I diabetes mellitus in Switzerland: steep rise in incidence in under 5 year old children in the past decade. *Diabetologia* 44, 286-289.
- Siemiatycki, J., Colle, E., Campbell, S., Dewar, R., Aubert, D., Belmonte, M.M., 1988. Incidence of IDDM in Montreal by ethnic group and by social class and comparisons with ethnic groups living elsewhere. *Diabetes* 37, 1096-1102.
- Spiegelhalter, D.J., Best, N.G., Carlin, B.R., van der Linde, A., 2002. Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society Series B-Statistical Methodology* 64, 583-616.

- Staples, J.A., Ponsonby, A.L., Lim, L.L.Y., McMichael, A.J., 2003. Ecologic analysis of some immune-related disorders, including type 1 diabetes, in Australia: Latitude, regional ultraviolet radiation, and disease prevalence. *Environmental Health Perspectives* 111, 518-523.
- Tarn, A.C., Gorsuch, A.N., Spencer, K.M., Bottazzo, G.F., Lister, J., 1983. Diabetes and social class. *Lancet* 2, 631-632.
- Torres-Aviles, F., Carrasco, E., Icaza, G., Perez-Bravo, F., 2010. Clustering of cases of type 1 diabetes in high socioeconomic communes in Santiago de Chile: spatio-temporal and geographical analysis. *Acta Diabetologica* 47, 251-257.
- Trewin, D., 2006. 1216.0 Australian Bureau of Statistics. Statistical Geography Volume 1 - Australian Standard Geographical Classification (ASGC).
- Vehik, K., Dabelea, D., 2011. The changing epidemiology of type 1 diabetes: why is it going through the roof? *Diabetes-Metabolism Research and Reviews* 27, 3-13.
- Waldhoer, T., Rami, B., Schober, E., Austrian Diabetes Incidence Study Group, 2008. Changing geographical distribution of diabetes mellitus type 1 incidence in Austrian children 1989-2005. *European Journal of Epidemiology* 23, 213-218.
- Waugh, N.R., 1986. Insulin-dependent diabetes in a Scottish region: incidence and urban/rural differences. *Journal of Epidemiology and Community Health* 40, 240-243.
- Yang, Z., Wang, K., Li, T.L., Sun, W., Li, Y.R., Chang, Y.F., Dorman, J.S., LaPorte, R.E., 1998. Childhood diabetes in China - Enormous variation by place and ethnic group. *Diabetes Care* 21, 525-529.

Appendices

Appendix 1: Country-of-origin of people in Western Australia, by census year.

	Census year				
	1991	1996	2001	2006	2011
People of European descent					
Australia (Non-Indigenous)	1,041,732	1,114,777	1,170,819	1,212,668	1,335,778
Canada	2,880	3,161	3,448	4,186	5,153
New Zealand	35,309	39,067	44,954	47,380	70,731
South Africa	9,363	10,683	15,337	22,221	35,329
United Kingdom	206,697	205,122	201,465	208,283	230,416
USA	5,824	5,511	6,031	6,947	8,854
Bosnia and Herzegovina				2,522	2,812
Croatia		4,220	5,196	5,218	5,154
Former Yugoslav Rep. of Macedonia		3,078	3,243		
France			1,694		
Germany	10,168	10,103	10,149	9,767	10,965
Greece	3,464	3,424	3,190	3,021	2,652
Hungary		1,389			
Ireland	9,491	9,468	8,948	8,935	14,293
Italy	26,986	25,117	23,074	21,204	19,482
Malta	1,070	1,058	1,030	899	997
Netherlands	11,684	11,008	10,543	10,140	9,982
Poland	7,192	6,930	6,469	5,799	5,565
Serbia and Montenegro		327			
South Eastern Europe				2,846	2,026
Turkey			736	798	1,045
USSR	2,546				
Yugoslavia	12,569		4,590	2,966	2,987
People of Asian descent					
Cambodia					1,017
China	3,136	4,547	5,242	7,920	16,685
Hong Kong	3,339	3,545	3,579	4,048	4,759
India	11,617	12,704	13,034	15,079	29,915
Indonesia		6,127	7,646	7,933	10,143
Japan				2,977	3,564
Malaysia	16,083	17,228	17,503	19,797	24,971
Philippines	3,762	4,809	5,334	6,886	17,233
Singapore		9,452	10,080	11,895	13,969
South Korea			1,339	2,127	4,097
Sri Lanka		2,731	3,005	3,290	5,342
Thailand				3,363	5,664
Vietnam	8,182	10,070	10,113	10,431	12,721
People not of European or Asian descent					
Chile		1,135			
Egypt		1,580	1,541	1,490	1,852
Fiji		664	609	678	1,035
Iraq				1,680	2,604
Lebanon	799	781	840	870	1,027
Papua New Guinea				1,348	
People excluded from population denominator					
Australia (Indigenous)	54,813	63,555	70,958	66,329	72,025
Country of origin not stated	96,698	119,513	160,315	215,371	246,327
Overseas visitor		13,128	19,274		
Total population	1,585,404	1,726,012	1,851,328	1,959,312	2,239,171

This shows the number of people in Western Australia, by country of origin, for each Australian Bureau of Statistics census from 1991 to 2011. We defined people of European descent as those born in Europe, born in Australia, or born in countries whose immigrants to Australia are typically of European descent.

Appendix 2: Model details.

The combined use of u and v follows Besag et al. (Besag et al., 1991). The heterogeneous random effect v_i was specified as being normally-distributed with a mean of zero and no constraint of correlation among neighbouring areas:

$$v_i = N(0, \sigma_v^2)$$

The spatially-correlated random effect u_i was based on a conditional autoregressive (CAR) term, with the constraint of following a normal distribution that is conditional on the local mean of CAR random effect estimates among neighbouring areas:

$$[u_i | u_j, i \neq j, \sigma_u^2] \sim N(\bar{u}_i, \sigma_i^2)$$

where
$$\bar{u}_i = \frac{\sum_j u_j \omega_{ij}}{\sum_j \omega_{ij}}$$

$$\sigma_i^2 = \frac{\sigma_u^2}{\sum_j \omega_{ij}}$$

$$\omega_{ij} = 1 \text{ if areas } i \text{ and } j \text{ are adjacent; otherwise } 0$$

Neighbours were defined as those areas immediately adjacent to the area in question, including neighbours which share only one vertex.

The spatiotemporal term, d_i , was based on the same CAR random effect structure as u_i , however there was no requirement that these two spatially-structured random effects d_i and u_i are correlated with each other.

Appendix 3. Summary information on the 36 Health Districts.

ID	remoteness	socioeconomic quintiles		population density (people per km ²)		population-weighted latitude		% of non-Indigenous population of European descent		% of children Indigenous	% 0-4 years	cases	person-years-at-risk	T1DM incidence
		1991	2010	1991	2010	1991	2010	1991	2010	20-year data				
1	Remote	2	2	161.7	255.7	-33.5	-33.6	92.8	84.0	7.7	32.6	13	66,019	19.7 (10.5-33.7)
2	Remote	4	3	1262.1	1067.9	-30.4	-30.3	88.7	80.5	17.0	37.7	30	164,546	18.2 (12.3-26.0)
3	Remote	2	4	1051.4	551.5	-21.4	-21.2	87.6	72.2	25.8	36.7	9	79,095	11.4 (5.2-21.6)
4	Remote	1	1	342.9	91.6	-16.5	-16.5	97.9	97.2	69.5	39.1	1	18,419	5.4 (0.1-30.2)
5	Remote	1	1	567.4	189.5	-17.8	-17.9	97.6	93.7	63.3	38.6	1	38,255	2.6 (0.1-4.6)
6	Remote	5	5	767.2	636.4	-21.3	-21.3	98.3	96.6	13.8	36.6	15	109,333	13.7 (7.7-22.6)
7	Rural	1	1	273.9	975.3	-24.1	-24.1	96.6	93.7	24.1	33.9	6	35,687	16.8 (6.2-36.6)
8	Rural	2	1	46.5	155.7	-27.1	-26.7	97.7	95.3	55.6	42.2	0	7,869	0.0 (0.0-46.9)
9	Rural	1	2	1035.5	796.8	-28.8	-28.8	94.3	92.6	13.5	31.4	23	138,972	16.6 (10.5-24.8)
10	Rural	3	2	95.3	87.3	-28.9	-28.8	91.0	90.6	12.0	33.6	11	58,364	18.8 (9.4-33.7)
11	Rural	3	3	1.6	1.1	-31.0	-31.0	98.5	96.4	3.4	31.9	13	43,198	30.1 (16.0-51.5)
12	Rural	2	2	120.2	83.9	-31.4	-31.4	89.6	85.4	9.0	31.8	33	130,243	25.3 (17.4-35.6)
13	Rural	4	2	111.4	185.2	-31.6	-31.6	95.2	91.2	7.4	34.7	8	61,557	13.0 (5.6-25.6)
14	Rural	4	3	102.8	95.6	-32.9	-32.9	96.2	94.9	7.7	32.6	27	87,475	30.9 (20.3-44.9)
15	Rural	5	4	385.1	258.1	-33.2	-33.2	93.7	91.4	2.8	30.3	21	129,937	16.2 (10.0-24.7)
16	Rural	2	3	1220.4	749.6	-33.4	-33.4	94.1	92.5	5.6	31.1	30	154,190	19.5 (13.1-27.8)
17	Rural	3	4	486.0	51.6	-33.7	-33.7	98.1	95.4	3.4	31.7	18	96,826	18.6 (11.0-29.4)
18	Rural	4	4	7.3	8.0	-34.0	-34.0	98.2	96.4	1.7	31.9	4	42,219	9.5 (2.6-24.3)
19	Rural	3	2	328.0	252.4	-33.4	-33.4	97.9	95.2	4.6	29.7	19	63,254	30.0 (18.1-46.9)
20	Rural	3	1	36.6	16.0	-33.9	-33.9	98.6	97.9	2.2	30.9	6	32,127	18.7 (6.9-40.6)
21	Rural	4	1	153.9	104.3	-34.4	-34.4	95.7	91.7	3.8	31.3	11	48,957	22.5 (11.2-40.2)
22	Rural	3	1	139.4	124.0	-33.8	-33.8	96.6	91.4	10.6	33.7	12	50,360	23.8 (12.3-41.6)
23	Rural	2	3	229.1	107.8	-34.8	-34.9	88.6	83.4	4.5	30.3	35	186,233	18.8 (13.1-26.1)
24	Urban	1	4	1866.9	1380.9	-31.8	-31.8	98.0	95.7	4.0	33.8	88	431,861	20.4 (16.3-25.1)
25	Urban	4	4	712.0	598.5	-31.9	-31.9	96.3	94.1	4.6	32.1	118	547,167	21.6 (17.9-25.8)
26	Urban	5	5	2203.4	1994.7	-31.8	-31.8	98.3	96.9	0.8	28.4	164	679,654	24.1 (20.6-28.1)
27	Urban	5	5	2052.2	2337.7	-31.9	-31.9	98.7	96.9	1.6	32.7	47	203,451	23.1 (17.0-30.7)
28	Urban	2	3	2285.4	2442.6	-31.9	-31.9	93.4	89.7	3.3	35.1	62	381,731	16.2 (12.5-20.8)
29	Urban	3	4	1949.2	2221.4	-31.9	-31.9	89.5	77.6	3.9	34.8	47	230,716	20.4 (15.0-27.1)
30	Urban	5	5	2228.7	2334.0	-32.0	-32.0	92.6	87.9	0.7	32.5	82	382,500	21.4 (17.1-26.6)
31	Urban	3	5	1926.4	2238.1	-32.0	-32.0	88.1	86.9	3.7	33.2	115	558,102	20.6 (17.0-4.7)
32	Urban	5	5	1129.4	963.0	-32.0	-32.0	98.0	96.6	3.0	28.9	49	209,321	23.4 (17.3-30.9)
33	Urban	5	5	1956.2	1963.6	-32.1	-32.1	98.5	96.5	2.4	31.7	157	740,113	21.2 (18.0-24.8)
34	Urban	4	3	1747.9	1336.5	-32.1	-32.1	94.0	80.9	4.7	32.4	137	667,411	20.5 (17.2-24.3)
35	Urban	1	3	1376.2	1327.8	-32.3	-32.3	94.5	90.1	3.6	32.9	97	439,841	22.1 (17.9-26.9)
36	Urban	1	2	439.2	485.8	-32.6	-32.6	98.1	96.5	3.8	30.0	62	251,032	24.7 (18.9-31.7)

Values for socioeconomic status (low = quintile 1; high = quintile 5), population density, population-weighted latitude and proportion of non-Indigenous population of European descent are provided for 1991 and 2010 to give an indication of changes over time. % children Indigenous = percentage of all 0-14 year olds of Indigenous descent; % 0-4 years = percentage of all 0-14 year old non-Indigenous children that were 0-4 years old; cases = number of cases of T1DM diagnosed from 1991-2010; population at risk = total number of person-years-at-risk among non-Indigenous 0-14 year olds; T1DM incidence = number of cases of T1DM per 100,000 person years at risk (unstandardised), with lower and upper

95% confidence interval. ID numbers 1-36 correspond to codes used in Figure 1. Indigenous children were excluded from the population at risk given that T1DM is very rare among Western Australia's Indigenous population (Glatthaar et al., 1988).