The changing incidence of childhood-onset type 1 diabetes in Wales: Effect of gender and season at diagnosis and birth

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A R T I C L E   I N F O

A B S T R A C T

Aims: Determinants of the changing incidence of childhood-onset type 1 diabetes remain uncertain. We determined the recent time-trend of type 1 diabetes incidence in Wales and explored the role of vitamin D by evaluating the influence of season both at diagnosis and at birth.

Methods: Data from all Welsh paediatric units 1990–2019, and from primary care to determine ascertainment.

Results: Log-linear modelling indicated a non-linear secular trend in incidence with peak and subsequent decline. The peak occurred around June 2010: 31·3 cases/year/100,000 children aged < 15y. It occurred earlier in children younger at diagnosis and earlier in boys. There were more cases in males aged <2y and >12y but more in females aged 9–10 y. More were diagnosed in winter. Also, children born in winter had less risk of future diabetes.

Conclusions: The risk of developing type 1 diabetes before age 15y in Wales is no longer increasing. The data on season are consistent with a preventative role for vitamin D both during pregnancy and later childhood. Metereological Office data shows increasing hours of sunlight since 1980 likely to increase vitamin D levels with less diabetes. Additional dietary supplementation with vitamin D might further reduce the incidence of type 1 diabetes.

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1.   Introduction

An increasing incidence of childhood onset type 1 diabetes (T1DM) both in Europe and worldwide is well documented. Finland and Scandinavian countries report the highest rates followed by UK registries [1]. The causative factors responsible for the very large differences in incidence rate between regions of the world and for the progressive increase in rates remain to be elucidated. Anecdotal reports from paediatric units across Wales suggested that our local rate of increase might have slowed. A change in this pattern of progressive increase may offer

some clue to the aetiological agents and mechanisms responsible.

The goal of research in this area is to be able to suggest factors which may be causative in the aetiology of type 1 diabetes. We investigated explanatory models examining the influence of age at diagnosis, sex and time trend on case numbers. Another factor related to incidence rate is season [2,3]. It has been suggested that perinatal factors influence the later development of T1DM. Therefore, we investigated the relationship of risk of T1DM to season at birth and season at diabetes diagnosis.

The specific aims of this study therefore were to

(1) document the incidence rate of childhood onset T1DM in Wales from 1990 to 2019.
(2) investigate the hypothesis that the incidence rate may no longer be increasing.
(3) assess the influence of sex at each year of age of diagnosis.
(4) compare the influence of season on risk of developing T1DM at diagnosis versus the influence of season at date of birth on the risk.

2. Methods

We studied incident cases of T1DM in Wales from 1990 to 2019 inclusive. Data were collected prospectively from 1995 by all paediatric diabetes units in Wales and adjoining English units that see children from Wales and a central register compiled. Patients were included if they developed T1DM before their 15th birthday whilst living in Wales. Three age groups were analysed: those developing diabetes before age five, aged five to nine and aged ten to fourteen years. Population data used for the offset (see below) were mid-year estimates derived from census data by the Office of National Statistics (ONS). In 2000 the total population of Wales was 2·89 million and those aged under 15 (U15) was 552,000.

2.1. Ascertainment

In 2006 all 530 GP practices in Wales were asked to send a list of children with diabetes under their care who would meet the inclusion criteria. A two source capture-recapture model was used to estimate the size of the total U15 diabetic population 1995–2005 [4]. The exercise was repeated in 2013 to cover the period 1990–2013. Since ascertainment was lower from 1990 to 94 all data were adjusted for ascertainment separately for each year of diagnosis, age group at diagnosis and sex.

2.2. Incidence rate over time

Log linear Poisson regression was undertaken, initially with age group at diagnosis, sex, age group-sex interaction, year of onset of diabetes (secular trend, period) and constant as fitted terms with natural log of denominator population as offset. An error distribution with dispersion factor 1 was assumed. A substantial improvement in fit was achieved with

the addition of a quadratic term (period squared). The best fit model included a two way interaction between age group at diagnosis and sex, and interactions between the linear component of the secular trend and age group, and between the linear component of the secular trend and sex. There was a quadratic interaction between secular trend (year of onset) and sex. The first derivative of the quadratic function was taken in order to identify the peak in cases for each sex and age group.

2.3. Effect of sex

Effect of sex was assessed at each individual year of age at diagnosis in order to understand in more detail the relationship of age and sex on risk of developing T1DM.

2.4. Effect of season

Season was defined as by The UK Meteorological Office: Winter from December to February, Spring: March to May, Summer: June to August, Autumn: September to November. Chisquare analysis was used to assess change in patient numbers according to season at birth and season at diagnosis. In order to account for the minor seasonal differences in birth numbers the expected numbers of births in each season was calculated according to the proportions seen in Wales 1996–2016 (data from ONS). Since winter was the largest contributor to the chi square statistic we compared number of cases diagnosed or born in winter as a proportion of the total by sex and by age group at diagnosis (under five years v five to fourteen years).

Data were analysed using GenStat® v13 (VSN International, Hemel Hempstead, UK).

3. Results

3.1. Ascertainment

We identified 4151 incident cases who developed T1DM in Wales before age 15 years from 1990 to 2019. Both ascertainment assessments for the periods 1995–2005 and 1995–2013 gave ascertainment >98% with ≥95% ascertainment in every calendar year. Ascertainment from 1990 to 1994 was 88%. Since ascertainment was lower in this first 5 year period all data (individually by age group at diagnosis, year of diagnosis and sex) were adjusted for ascertainment. The incidence rates for all children aged under 15 years and for the three separate age groups at diagnosis for 1990–2019 are shown in Figs. 1 & 2.

3.2. Modelling the incidence rate

Modelling with the assumption of compound annual growth adjusted for sex and age group at diagnosis indicated 1·8 (95% CI 1.4–2.1)% per annum compound growth in incidence rate over the whole period 1990–2019. Although significant (p < 0.001), the compound growth model produced an unacceptable fit with mean residual deviance (MRD) 1·91. The non-linear model (including the quadratic term) significantly
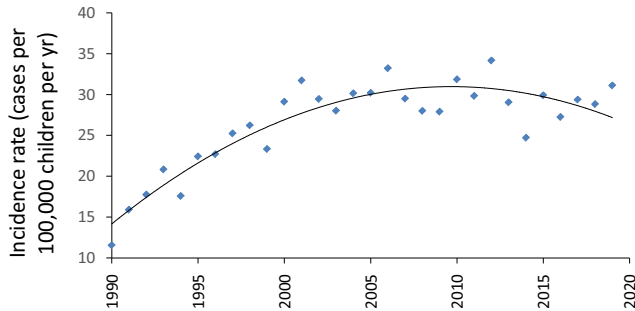
Fig. 1 – The annual incidence rate per 100,000 children of T1DM in children aged under 15 years at diagnosis in Wales 1990–2019. Data are corrected for ascertainment but are otherwise unadjusted.
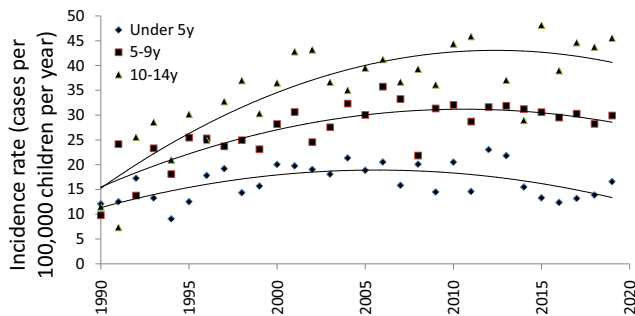
Fig. 2 – The annual incidence rate per 100,000 children of T1DM in children aged under 5 years (◆), 5–9 years (■) and 10–14 years (▲) at diagnosis in Wales 1990–2019. Data are corrected for ascertainment but are otherwise unadjusted.

improved the model fit with lower MRD of 1·46. The significant factors in the model are listed in Table 1. The quadratic term was negative indicating numbers peaked then declined. The interaction between age group at diagnosis and the linear component of the secular trend (year of diagnosis) was strongly significant (p < 0·001) indicating different changes in the slope of the incidence rate over time. The interaction

between sex and the linear component was also significant (p = 0·018). We therefore estimated the date of peak case numbers for each sex and age group at diagnosis separately (Table 2). The quadratic term was not different between age groups indicating a similar curvilinear trend in children diagnosed at all ages. For the total cohort the date of peak incidence was June 2010 when calculated from a model without the interactions of gender and age group at diagnosis with the linear and quadratic components of the secular trend (MRD 1·58). The peak annual incidence rate of childhood T1DM in Wales was 31·3 cases per 100,000 children aged under 15 years.

3.3. Influence of sex

51·7% of the cases in this analysis were male. The relative proportions of male and female cases at each year of age at diagnosis is shown in Table 3. The 95% confidence intervals (Poisson) indicate there are significantly >50% males diagnosed before age two and after age 12 years. At age nine to ten years there are significantly more cases of T1DM in girls. Paediatric clinics also reported cases diagnosed after their 15th birthday. These show that the male preponderance persists beyond age 15 years (shown in Table 3).

3.4. Effect of season at diagnosis and at birth

Table 4 shows the numbers of cases diagnosed by season of diagnosis and by season of birth. Season of diagnosis shows marked variation with more diagnoses of T1DM in both sexes made in winter and less in spring and summer (χ^2 = 30·1, 3df, p < 0·001). The season of birth shows a different pattern with lower numbers of future diabetic patients being born in winter & more in spring (χ^2 = 9·1, p < 0·05). The increased number of cases diagnosed in winter is more apparent in males: 29·5% of male cases versus 27·0% of female cases were diagnosed in winter, a difference in proportion of 2·5 (95%CI −0·2 to 5·3)%. The effect of season of birth is more apparent in females with the number of subsequent cases born in winter comprising 23·8% of males but 21·4% of females, a difference of 2·4 (-0·1

Table 1 – Estimates of parameters of the model to predict case numbers. For Age group at diagnosis the reference level is Age Group 0–4 so estimates for the older age groups give the change in relation to the 0–5 year olds. Similarly with sex where the reference level is male so coefficients estimate the difference in females.

Parameter	Estimate	SE of estimate	t	t probability	Antilog of estimate
Constant	−8·6037	0·0540	−159·32	<0·001	0·0001834
Age 10–14	0·6836	0·0623	10·98	<0·001	1·981
Age 5–9	0·3396	0·0661	5·14	<0·001	1·404
Sex female	−0·0686	0·0735	−0·93	0·350	0·9337
Age 10–14*Sex female	−0·0988	0·0822	−1·20	0·230	0·9059
Age 5–9*Sex female	0·1591	0·0861	1·85	0·065	1·172
Secular trend linear	0·02852	0·00558	5·11	<0·001	1·029
Secular trend quadratic	−0·002443	0·000340	−7·19	<0·001	0·9976
Linear trend*Sex female	−0·01452	0·00615	−2·36	0·018	0·9856
Quadratic trend*Sex female	0·001216	0·000480	2·53	0·011	1·001
Linear trend*Age 10–14	0·02282	0·00500	4·56	<0·001	1·023
Linear trend*Age 5–9	0·01405	0·00519	2·71	0·007	1·014

Table 2 – Date of peak incidence of cases for boys and girls in the three Age groups at diagnosis of diabetes.

Age group at diagnosis and gender	Date of peak incidence
Boys aged 0–4 years	April 2006
Boys aged 5–9	March 2009
Boys aged 10–14	January 2011
Girls aged 0–4	March 2006
Girls aged 5–9	November 2011
Girls aged 10–14	July 2015

Table 3 – Children With T1DM diagnosed 1990–2019 and the proportion male, according to age at diagnosis.

Age at diagnosis (years)	Cases (number)	Proportion male (%)	95% CI
<1	29	69	52, 86
1–2	162	56	49, 64
2–3	212	50	44, 57
3–4	206	51	45, 58
4–5	238	47	41, 54
5–6	212	50	44, 57
6–7	267	50	44, 56
7–8	271	51	45, 57
8–9	347	49	44, 54
9–10	340	42	37, 47
10–11	432	46	41, 51
11–12	398	46	41, 51
12–13	429	59	54, 63
13–14	335	61	56, 66
14–15	273	66	60, 71
15–16	211	64	58, 71
>16	82	56	45, 67

to 5·0)%. Comparison of the different age groups at diagnosis showed no differences by season.

4. Discussion

The capture-recapture analyses of ascertainment appear valid in that the sources were independent, both sources provided coverage across the Principality and there were no unusual areas of missing data identified. All calendar years from 1995 to 2013 had adequate ascertainment ≥95%. Thus, changes in the incidence rate do not appear to be due to missing data. Introduction of the quadratic term improved model fit substantially indicating that the time trend in T1DM incidence is no longer linear. Clearly, simple linear estimates of compound growth overestimate future numbers of cases.

This analysis finds that the incidence rate of childhood-onset T1DM in Wales shows a peak and subsequent decline. All three age groups at diagnosis show a similar curvilinear trend (no interaction between age group and quadratic component of secular trend) but the peak occurs earlier with younger age at diagnosis. This is consistent with influences in pregnancy or early life. Previous studies have shown a faster increase in incidence before age five years [5], although this is no longer seen [1]. In children diagnosed after age five we find the peak was reached sooner in boys than girls indicating hormonal influences on development of T1DM.

We found a peak incidence rate in Wales of 31.3 new cases per 10^5 under 15 year old children per annum. This is a high rate in comparison with most countries but not dissimilar from Scandinavian regions [1]. The finding that the incidence rate of childhood-onset T1DM in Wales is no longer increasing and has already peaked is novel. International data up to 2013 show a continuing increase [1]. In children aged <15 years the Norway national register reported a plateau in incidence rate at 22·4 new cases/10^5 children per annum over the period 1989–1998 but the rate subsequently increased and

Table 4 – Numbers of Cases of T1DM diagnosed 1990–2019 according to season of diagnosis and season of birth. More cases were diagnosed in winter (χ^2 = 301, p < 0001). Less cases had been born in winter (χ^2 = 91, p < 005). In 23 cases the month of diagnosis was not recorded.

Season	Cases of T1DM by season at diagnosis (number)	Cases of T1DM by season of birth (number)
Winter	1169	940
Spring	989	1086
Summer	930	1063
Autumn	1040	1062

was 33·1 from 2004 to 8 with little or no change 2004–2012 [6,7]. Thus the reduction in trend growth we identify may also change going forward. Regional differences have been described in Norway and Spain indicating that the generally reported increase in incidence that has been described may not be as uniform as supposed [6,8]. The most recent EURO-DIAB data show rates continue to increase in countries with lower incidence but that there is a slowing of the rate of increase in regions with the highest incidence [1]. Registries in Ireland, Sweden, Norway and Finland have recently identified such a slowing of the incidence rate [9–12]. Data from the USA shows a continuing annual increase of 1·4% 2002–2012 [13].

The overall male preponderance was small (51·7% of the total), as shown in other reports, so sex alone is not a significant predictor of incidence in the model. However, the incidence varies quite markedly with sex at different ages (Table 3). T1DM before age two and after age 12 years was more common in males. Testosterone levels in male infants peak at 6–12 weeks of age and decline slowly from three months [14]. At age nine to ten years at the time of female puberty T1DM was more common in girls. Thus analysis of patient numbers by individual year of age at diagnosis suggests an influence of sex hormones clearly evident at male and female puberty. An effect of sex hormones is also implicated in the earlier peak incidence seen in older boys versus girls (Table 2).

Although peak incidence of T1DM occurs in mid childhood, immunologic, morphologic and metabolic data indicate there is a prolonged prodromal period of at least five years before the clinical disease manifests [15]. Islet autoantibodies are often present before two years of age [16]. Twin studies and analysis of HLA alleles indicate that genetic factors contribute but environmental influences are the only possible explanation for recent changes in incidence. The proportion of cases with high risk alleles in the HLA region has been decreasing as the number of cases increase suggesting an increasing importance of environmental factors [17–19].

A variety of factors in early life are associated with increased risk of childhood T1DM. These include increasing maternal age, pre-eclampsia, viral infections during pregnancy, lower gestational age, increasing birth weight, caesarian delivery and neonatal jaundice due to blood group incompatibility [20–28]. Breast feeding and increasing birth order reduce risk, particularly for onset before age 5 years [20,22]. It has been suggested such events influence maturation of the immune system and subsequent β-cell toxicity [21]. The modern western lifestyle seems associated with greater incidence of T1DM. There is a relationship with the increased height and weight of children [29]. Increased insulin resistance may be a factor in T1DM as well as type 2 (the Accelerator hypothesis) [30]. Childhood infections were thought to protect against T1DM (the Hygiene hypothesis) but recent analyses from Germany and Taiwan show that respiratory and enterovirus infections respectively increase the risk of T1DM [31,32].

We investigated the influence on incidence rate of season both at diagnosis and at birth. An effect is apparent at both but clearly greater at the time of diagnosis. There may be differences by sex but the results were of borderline statistical

significance here. Variation in case numbers with season may be via the effect of sunlight on vitamin D levels. Approximately 90% of circulating vitamin D is generated in the skin following exposure to UVB in sunlight. More cases presenting during winter is consistent with a protective effect of vitamin D with levels being lower in winter due to less sun and UVB exposure. Lower numbers of cases were seen in children born in winter. If this is also an effect of vitamin D it implies the protective effect is operative 6 months earlier during pregnancy rather than at the time of birth. The SEARCH for Diabetes in Youth Study found similar results in the USA with less cases of T1DM in children that had been born in winter as did UK data 1974–88 although not in the rest of Europe [2,3,33]. We show that this effect continues in the UK. The earlier peak in incidence in the under five year old group is consistent with the influence of seasonal change in vitamin D during pregnancy. Interestingly, the effect was not seen in more southerly US latitudes where there might be good sun exposure all year round [2].

The evidence (in man) suggesting a role for vitamin D in the development of T1DM comes from several sources. A preventative effect of vitamin D consequent on sunlight exposure seems likely to contribute to the very marked variation in incidence of T1DM with latitude, from 1 to 3 cases per 100,000 children in China and some Asian and South American nations to 30–60 per 100,000 in Scandinavia [1,34]. Secondly, polymorphisms in genes encoding proteins involved in Vitamin D metabolism are claimed to associate with T1DM. Variants at the Bsm-I and Fok-I loci on the Vitamin D receptor gene associate with T1DM. Polymorphisms in the gene encoding the Vitamin D binding protein (VDBP, the circulating transporter for 1,25 dihydroxyvitamin D) are also thought to be related to T1DM incidence. T1DM patients have lower circulating levels of VDBP than control subjects. Polymorphisms in the genes for 25α-hydroxylase and 1α-hydroxylase are also thought to influence T1DM incidence. There are some inconsistencies in these studies which may reflect the interaction between genetic and environmental factors [35]. Thirdly, many studies confirm the effect of vitamin D on adaptive immunity with induced immunological tolerance and anti-inflammatory effect exerted via its effect on gene transcription in macrophages, dendritic cells, CD4+ and CD8+ T cells and B cells with altered synthesis of a number of cytokines [35]. Fourthly, vitamin D levels in newly diagnosed patients versus controls have been lower in most countries: Sweden [36], Italy [37,38], Australia [39], India [40], the USA [41,42], and Kuwait [43], but not all namely Finland [44,45], and the USA [46]. Fifth, Vitamin D supplements are sometimes given in pregnancy and infancy so the influence of 25(OH)D levels both in the mother during pregnancy and in early life on the later incidence of T1DM in the child have been studied. Benefit from supplementation during pregnancy with vitamin D [47], or cod liver oil was seen in Norway [48]. In Denmark, increased hours of sun exposure during pregnancy predicted a lower incidence of T1DM [49]. But no difference in first trimester 25(OH)D levels between future T1DM cases and controls was seen in Finland [50], or when measured at delivery in Italy [51], although case numbers in the Italian study were small. Oral vitamin D during the first year of life substantially reduced T1DM

incidence in Finland [52], and also in a EURODIAB multicentre analysis [53].

Vitamin D deficiency is common in northern latitudes. In the USA, NHANES data 1988–2010 show overall 14–18% of the under age 40y population had 25(OH)D levels <40 nmol/l [54]. In Sweden (1982–2013) 34% of children aged 1-18y had serum 25(OH)D < 50 nmol/l and 3% were <25 nmol/l [55]. The data does not show a progressively increasing prevalence of vitamin D deficiency but that may not be necessary for a continuing linear increase in T1DM incidence trend. Data from the UK National Diet and Nutrition Survey (NDNS) rolling programme 2009/10 and 2012/13 found a high prevalence of vitamin D deficiency in Wales: 23% of 11-18y olds had a 25 (OH)D level <25 nmol/l [56]. For the UK as a whole a slightly lower proportion is deficient. Lower levels of 25(OH)D are seen in diabetic children (v controls) in countries with more sun (Australia, Kuwait, Qatar) as well as at northern latitudes [39,43,57].

There is marked seasonal variation in 25(OH)D levels. Manchester (UK) data showed levels highest in September: mean 25(OH)D 60 nmol/l, and lowest in January at 38 nmol/l [58]. NDNS found 25(OH)D levels < 25 nmol/l in 31% children aged 4-10y from Jan-March and in 40% of children aged 11-18y. From July to Sept the proportions deficient were 2% of the younger and 13% of the older children [56]. Season therefore brings about significant changes in 25(OH)D levels similar or greater than those associated with the diagnosis of T1DM in the studies quoted above.

Changes to sunlight exposure and circulating vitamin D concentrations could contribute to recent changes in incidence rate. In Wales, data from the UK Metereological office shows that the annual hours of sunlight have shown an increasing trend since 1980 (Fig. 3) in total providing approximately 2 h more sun per week. Their data also show an increase in mean annual temperature in Wales (data not shown) perhaps encouraging families to spend more time outdoors. Little synthesis of vitamin D takes place during the winter months in northern climes. The lower circulating

levels are maintained by dietary intake and possibly release of vitamin D from stores in adipose tissue. It has been estimated that a 25(OH)D level of 80.5 nmol/l is needed in Sept. to maintain the plasma level > 25 nmol/l throughout the winter in white caucasians. With 35% skin area exposed (equivalent to shorts/skirt and T-shirt) around noon from March to September the daily sun exposure time to reach the above target (80.5 nmol/l) in September is estimated at 9 min [59]. Thus, the additional hours of sunshine in Wales since 1980 are enough to increase vitamin D levels sufficiently to alter susceptibility to T1DM.

No clear pattern of change in dietary vitamin D (excluding supplements) or 25(OH)D levels in Wales was identified by NDNS comparing 2016/17 with 2008/9 but this is mainly after the times of peak incidence we identify [60]. We lack vitamin D data from the youngest children. The seasonal variation implies an effect of vitamin D over a few months, presumably on top of underlying susceptibility. Dietary supplementation with vitamin D is now recommended in the UK and particularly Wales (WHC/2016/043) [56,61].

4.1. Conclusion

The previously increasing time trend in the incidence rate of childhood onset T1DM in Wales is shown to have peaked with recent decline. Peak incidence rate occurred earlier in children who were diagnosed with diabetes at younger age and earlier in boys than girls. Multiple factors influence the risk of developing T1DM. Most cannot continue to increase indefinitely such that a peak in incidence would be expected. Season of the year has a clear influence on case numbers, both season at birth and at diagnosis. This provides support for the hypothesis that vitamin D both in pregnancy and later in childhood helps prevent childhood T1DM. Metereological Office data show that the annual hours of sunlight in Wales have been increasing since 1980. The increased hours of sunlight are sufficient to increase vitamin D levels from the low levels seen in winter and in T1DM at diagnosis. This and more
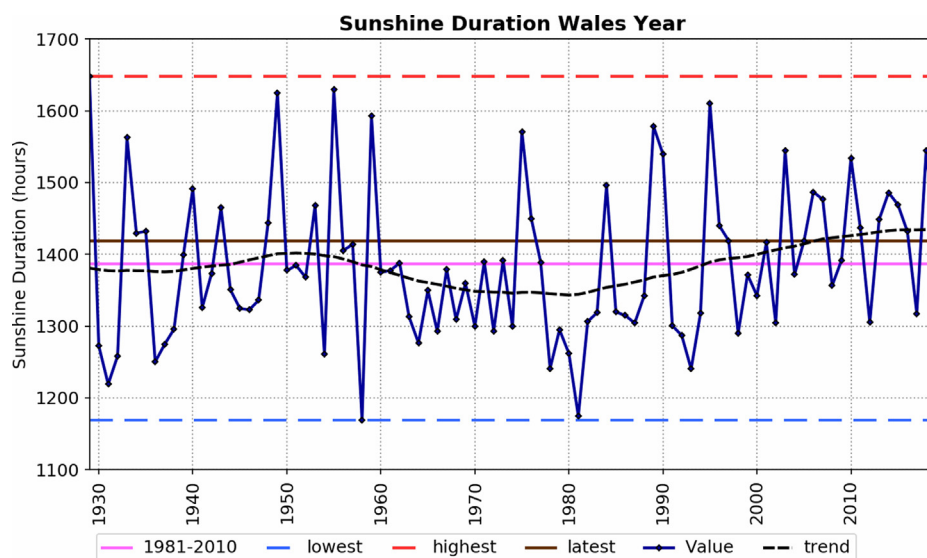

Fig. 3 – Annual duration of sunshine (hours) in Wales (© Crown copyright Metereological Office, with permission).

dietary supplementation may be factors reducing the incidence of T1DM in Wales. These data are not conclusive but provide further support for more widespread dietary supplementation with vitamin D in the UK and northern latitudes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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